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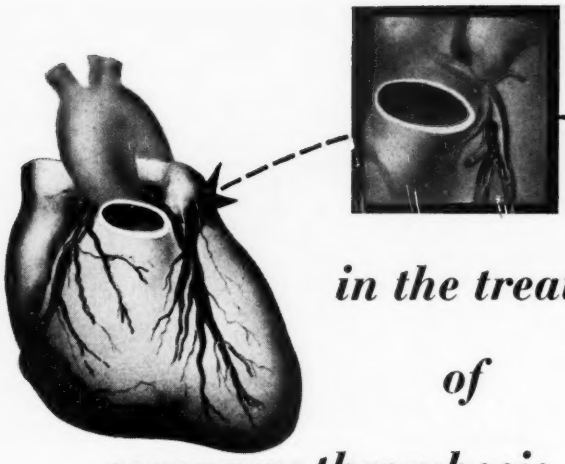

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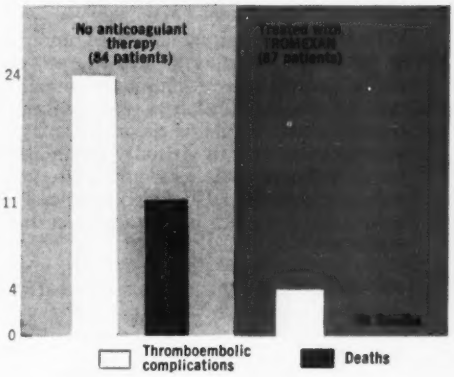

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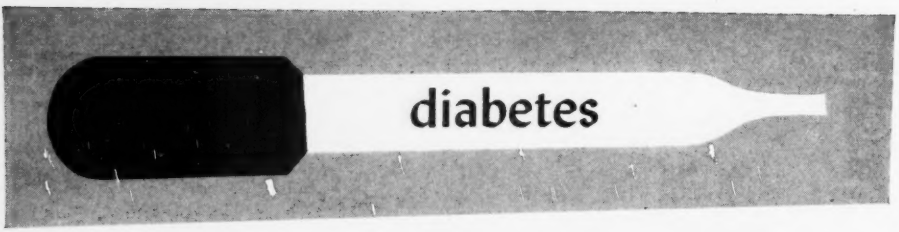

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METASTATIC CALCIFICATION AND NEPHROCALCINOSIS FROM MEDICAL TREATMENT OF PEPTIC ULCER

ISIDORE SNAPPER, M.D.
CHICAGO
LIEUTENANT COLONEL WILLIAM G. BRADLEY
MEDICAL CORPS, UNITED STATES AIR FORCE
AND
VERNON E. WILSON, M.D.
CHICAGO

INTEREST in the problem of the deposition of calcium in abnormal locations, that is, in subcutaneous tissue and visceral organs, has been revived by the relatively recent publication of Burnett and associates of a study of six cases of metastatic calcification related to excessive ingestion of alkali and milk in patients with ulcers of the stomach.[6]

GENERAL COMMENTS ON METASTATIC CALCIFICATION

Metastatic calcification may be caused by many different conditions in addition to that listed above, and the following ailments should be mentioned: (1) administration of excessive amounts of vitamin D; (2) hyperparathyroidism; (3) chronic renal disease in young persons, leading to long-standing acidosis; (4) complete immobilization in patients with fractures treated with extensive plaster casts or during wide-spread paralysis in poliomyelitis; (5) chronic lower nephron nephrosis or so-called tubular acidosis.[17]

Metastatic calcification also occurs in rapidly spreading osteolytic malignant lesions of the skeleton. The tendency to metastatic calcification is considerably increased by the therapeutic administration of testosterone in patients with skeletal malignant disease and preexisting renal damage.[18]

Clinical analysis indicates that different mechanisms must play a role in the causation of this syndrome.* Metastatic calcification in hypervitaminosis D, in hyperparathyroidism, in complete immobilization of young persons, and in wide-spread osteolytic metastatic disease of the skeleton is generally accompanied by hypercalcemia.† When, however, abnormal calcium deposition in the tissues occurs in young persons with long-standing renal insufficiency with acidosis, then a decrease of the calcium content of the serum is commonly found. The same hypocalcemia occurs in nephrocalcinosis as seen in tubular acidosis.

The levels of the inorganic phosphorus of the serum also vary in different forms of metastatic calcification. In renal insufficiency there is hyperphosphatemia, but in

From the Department of Medicine, University of Illinois School of Medicine, Research and Educational Hospitals.

* References 4 and 11.

† References 1, 13, and 18.

chronic hyperparathyroidism the serum phosphates are decreased, unless marked renal failure is present. Even the pH of the urine is unreliable as a criterion for the prediction of nephrocalcinosis. Acid urine is excreted in young persons suffering from chronic uremia, but in hyperparathyroidism and chronic tubular acidosis an alkaline urine is produced. It follows that metastatic calcification can occur (1) in the presence of high serum calcium and high inorganic phosphate (hypervitaminosis D, rapidly spreading skeletal malignant disease, hyperparathyroidism with uremia) or (2) in the presence of hypocalcemia and high inorganic phosphate (chronic uremia) or (3) in the presence of hypercalcemia and hypophosphatemia (hyperparathyroidism).

Thus it would be difficult to explain metastatic calcification by oversaturation of the tissue fluids with calcium phosphate; local conditions of the tissues in which the calcium will be deposited must certainly play an important role.

In general, it can be said that calcium is deposited preferentially in organs where the excretion of acid results in a temporary tissue alkalosis. Such an alkalosis would favor the precipitation of calcium phosphate and calcium carbonate. This would explain why metastatic calcification is so frequently seen in the kidneys, where acid phosphates are excreted; in the stomach, where hydrochloric acid is produced, and in the lungs, where carbon dioxide is removed. On the other hand, this explanation cannot be generally applied, because in the heart muscle and in the subcutaneous tissue calcinosis is also frequently observed. It has already been noted that in certain conditions, such as chronic uremia in young persons, deposition of calcium salts occurs often in the subcutaneous tissue, especially near the joints, giving rise to a clinical picture which is often mistaken for acute or subacute rheumatoid arthritis.

Age plays an important role in some forms of metastatic calcification. In chronic uremia and also in immobilization, deposition of calcium in soft tissues and visceral organs seldom occurs except in young persons. However, in the higher age group hyperparathyroidism or wide-spread skeletal malignant disease often causes metastatic calcification.

Finally, the condition of the kidney should be considered. As mentioned above, hypercalcemia and metastatic calcification due to rapidly spreading malignant disease of the skeleton probably only occur if there has been preexisting renal damage. In hyperparathyroidism, however, metastatic calcification develops in persons who had previously completely healthy kidneys.

METASTATIC CALCIFICATION AFTER SIPPY DIET OF LONG DURATION

Clinical experiences with hyperparathyroidism have already proved that dietary influences should not be underestimated in the causation of metastatic calcification. It is well known that the subjective complaints of patients with hyperparathyroidism can be improved by the administration of large amounts of calcium and phosphate. Nevertheless, this treatment should not be tried in patients with hyperparathyroidism, because during ingestion of calcium phosphate nephrocalcinosis develops much more rapidly than when such patients are kept on a low-calcium diet. The clinical observations collected by Dubois and his associates during the study of the very first patient with hyperparathyroidism ever reported in the United States emphasize the rapidly developing nephrocalcinosis in hyperparathyroidism under the influence of a diet high in calcium and phosphate.[8]

In addition to the metastatic calcification caused by excessive ingestion of alkali and milk, treatment of ulcer patients with Sippy diet and powders has been known to cause acute alkalosis with severe polyuria and mental confusion.‡ In such cases, the CO_2-combining power of the serum rises to very high levels, and more or less pronounced hypercalcemia and retention of water are usually present. When use of the Sippy diet and powders is stopped, these signs usually disappear in a few days.

Pathological calcification and stone formation in conservatively treated ulcer patients may be found to be a part of a general metabolic pattern. Support for this theory is lent by work done on citric acid excretion in humans and on formation of renal stones in rats.

In essence, Shorr has been able to demonstrate markedly increased citric acid excretion in humans on a high alkali intake.[16] This has thrown light on the older experiments of A. Polak.[15] The latter, in a very thorough piece of investigation, was able to demonstrate that addition of calcium carbonate to a fixed diet leads to the formation of kidney and bladder stones in young male rats. By careful quantitative and qualitative chemical tests these concrements were identified as calcium citrate stones. This stone formation was obtained by the addition of 3% calcium carbonate to the diet and did not appear when equivalent quantities of potassium phosphate or of calcium chloride were substituted for the calcium carbonate. In all cases, using calcium carbonate, the urine was found to have a relatively high pH, the range being 7.1 to 8.5 (with one exception). The rats who were kept on a calcium chloride diet excreted urine with a pH in the range of 5.6 to 6.5. Thus, while in Polak's experiments the influence of the calcium carbonate ingestion on citric acid excretion in the rats was not directly checked, it would seem that the formation of calcium citrate stones in kidneys and bladder would be caused on one hand by the large amounts of calcium ingested and on the other hand by the excretion of citrate caused by chronic alkalosis. It is interesting to note that the increased citrate excretion appears to be a physiological mechanism which increases the solubility of the calcium compounds excreted, but this mechanism is probably overloaded in the above experiments, resulting in the deposition of calcium citrate.[10]

Some years ago, Butler found that mice given an alkaline diet for 8 to 14 days developed calcium deposits in lungs, stomach, and kidneys.[7] In these experiments, pH of urine and alkali content of the diet were not recorded.

It thus becomes readily apparent that the sequelae of a Sippy diet continued for several years may be due partly to the calcium carbonate and calcium phosphate accumulated in the blood and partly to the excretion and deposition of the ingested salts. However, the changes of metabolism which take place under the influence of the chronic alkalosis should not be underrated.

In such patients with hypercalcemia, often accompanied by metastatic calcification, without hypercalciuria or hypophosphatemia, marked renal insufficiency with azotemia may develop.[6] Hyperphosphatemia is commonly a part of this syndrome, due in part to the uremia and in part to the phosphate content of the milk. This indicates that not only the calcium but also the phosphorus of the milk may play a role in the production of this syndrome. Metastatic calcification is usually present

‡ References 9 and 12.

in subcutaneous tissue, but it often also involves visceral organs, especially the kidneys. The urinary calcium excretion is nearly always within normal limits and may even be low.

The differentiation of this condition from hyperparathyroidism is usually easy, since hypophosphatemia and hypercalciuria are absent. In addition, after withdrawal of milk and Sippy powders, the serum calcium and phosphates often return to normal. In hyperparathyroidism the serum calcium is not easily influenced by such dietary changes.[2]

Metastatic calcification in patients with long-standing uremia usually develops in young persons in whom the serum calcium is nearly always lower than normal and the hyperphosphatema is excessive. In such cases, dietary measures have little or no influence upon the calcium and phosphorus contents of the serum.§

REPORT OF CASES

We here report two additional cases of metastatic calcification in ulcer patients. In both cases a large amount of a proprietary salicylic preparation (Alka-Seltzer) was ingested. However, in Case 1 the daily ingestion of calcium was very high, while in Case 2 the amount was actually lower than the recommended daily requirement. We believe that our second case is a rarity, and this experience indicates that alkalosis alone without a high ingestion of calcium may lead to metastatic calcification and hypercalcemia.

CASE 1.—A 62-year-old man was recently observed who for the previous 15 months had been suffering from generalized bone and joint pains. Over the same period of time painless masses had developed in the left index finger, the area of the left radius, and the area of the right olecranon. At first, the pains responded to rest and massage, but gradually the condition deteriorated, and finally the pains became unbearable.

An original workup revealed only anemia, for which the patient was transfused. Because his pain became progressively severer, he was sent to another hospital, where a workup revealed calcific deposits in the muscles and kidneys, elevated blood urea nitrogen, hypertension, and anemia. Parathyroid surgery was planned, but because of severity of his symptoms he was two weeks later admitted to the Mount Sinai Hospital, in New York. There was no known hypertension 15 months previously. For the past year he had had frequent urination, every two hours, and he had suffered from anorexia for one year. At the same time the left eye had become progressively blind. The patient had a history of asthma for over 40 years, for which he had received the usual medications. For 10 years he had treated a peptic ulcer by the consumption of large quantities of milk, about 3 qt. (2.85 liters) per day. Concomitantly, he had taken Alka-Seltzer in such large amounts that he had bought the latter preparation wholesale.

On admission, pulse, temperature, and respiration were normal. The blood pressure was 115/80. The patient was frankly uremic and pale, with dry yellowish skin and a uremic odor to the breath. There was a rubbery nontender 8 by 8 by 3 cm. mass in the left infraclavicular fossa, another, 1.5 cm., mass over the distal phalanx of the left index finger, and a third mass over the right olecranon process. Ophthalmological examination revealed retinal findings consistent with arteriosclerosis and Grade II hypertension. On auscultation of the lungs, variable breath sounds were heard, with occasional coarse and musical rales at the right base. There was slight depression of breath sounds over the left lung without alterations in the percussion note. The heart was enlarged to the left by percussion. Heart sounds were distant, with the second aortic sound equal to the second pulmonic sound. There were no significant murmurs, rubs, or gallops. The abdomen was distended. The liver could be percussed one fingerbreadth below the costal margin. The spleen and kidneys were not felt. No ascites was present. Results of the genital and rectal examinations were within normal limits. Occasional twitching motions

§ References 5 and 14.

Fig. 1 (Case 1).—Painless mass in the left index finger.

Fig. 2 (Case 1).—Swelling of right elbow from metastatic calcium deposition.

Fig. 3 (Case 1).—Swelling about the left shoulder due to amorphous calcific deposits.

of the hands were present. There was atrophy of the muscles of the extremities, with pain on motion of most joints. The patient was unable to turn over in bed because of pain, although no areas of specific bone tenderness were found.

The urine showed a specific gravity varying between 1.010 and 1.016, with an acid to alkaline reaction and a 3 to 4 + reaction for albumin. On microscopic examination rare blood cells and occasionally many white blood cells were found. The qualitative reaction for calcium (method of Sulkowitch) was negative. The Wassermann and Kahn tests were negative. Examination of the blood disclosed 10.1 gm. of hemoglobin per 100 cc., a red blood cell count of 3,450,000 per cubic millimeter, and a white cell count of 10,000 per cubic millimeter, with 81% neutrophiles, 4% nonsegmented neutrophiles, 9% lymphocytes, 6% monocytes, and 1% basophiles. The sedimentation rate was 120 mm. in an hour. Blood chemistry studies showed a moderate increase of blood urea nitrogen, 53 mg. per 100 cc.; marked acidosis; CO_2-combining power 33 vol. %; markedly increased creatinine, 11.6 mg. per 100 cc., and inorganic phosphate 11.0 mg. per 100 cc. The uric acid was 5.3 mg. per 100 cc.; calcium, 9.3 mg. per 100 cc.; chlorides, 550 mg. per 100 cc.; alkaline phosphatase, 12 King-Armstrong units; sodium, 128 mEq. per liter; potassium, 3.9 mEq. per liter; serum albumin, 2.1 gm. per 100 cc., and serum globulin, 2.9 gm. per 100 cc. Staphylococcus albus B was grown in a culture from the urine. Radiologic examination showed nodular infiltrations throughout both lungs, suggestive of bronchopneumonia. The roentgenograms of the skull were normal. Widespread nephrocalcinosis was found. The soft tissues about the shoulders, elbows, and hips contained amorphous calcific deposits. There were mild changes of degenerative arthritis in the joints. The arteries of the upper extremities were calcified. Electrocardiogram showed left axis deviation; the QT interval was prolonged to 0.40 second, as may be seen in uremia. Repeat ECG showed nodal bradycardia, with occasional sinus beats and intraventricular block.

The patient was in the hospital for 10 days and was afebrile until his last two days. After his third hospital day he was noted to be anuric, and he so remained until his death, on the 10th hospital day. Cystoscopy was performed on Dec. 18. The catheters were passed with ease in both ureters. No flow was noted from either ureteral orifice. Ophthalmological examination revealed the presence of several superficial infiltrates in the cornea at the limbus. It was not certain whether or not this represented an early arcus senilis. Some calcific deposits were also noted in the conjunctiva.[19] The blood urea nitrogen rose gradually to 120 mg. and his serum chloride fell to 480 mg. per 100 cc. (as sodium chloride). On his last three hospital days he had epileptiform seizures, and he died on his 10th hospital day. A few weeks before admission his physicians had forbidden him to drink milk, because it had been evident that milk had some connection with the uremia. This may well have been the reason why on admission the calcium of the serum had come down to normal values. The subcutaneous calcinosis was extensive in the bones of both humeri, the elbow, and the chest wall. In addition, there was widespread peripheral calcification of the arteries; there was probably no real arteriosclerosis, but there were calcium metastases into the media of arteries.

Case 2.—A 65-year-old white woman developed symptoms suggestive of a possible peptic ulcer in 1938 and placed herself on a meat-free alkaline-ash type of diet, which she had followed ever since. In 1945 she first developed severe paroxysms of coughing, which occurred several times daily and often led to vomiting and pain in the substernal and epigastric areas. Alka-Seltzer was found to be quite effective in relieving this pain, and for the past eight years she had been taking on the average of three tablets daily. In 1949 metastatic calcifications in the subcutaneous tissues and in the kidneys were first discovered on x-rays. Laboratory findings at this time were as follows: blood urea nitrogen was 31.7 mg.; creatinine, 2.1 mg.; nonprotein nitrogen, 54.5 mg.; serum globulin, 4.53 gm.; serum albumin, 1.7 gm.; serum calcium, 10.3 mg., and serum phosphorus, 5.5 mg. per 100 cc., and serum alkaline phosphatase was 12.0 units (King-Armstrong).

In August, 1952, serum calcium was 12.05 mg. and serum phosphorus was 5.9 mg. per 100 cc.

In October, 1952, x-rays revealed metastatic calcification involving both kidneys, the ascending and descending aorta and its branches, and both femoral arteries. There were also subcutaneous calcifications superior to both greater trochanters, in areas superior to both scapulae, and in the soft tissues of the neck.

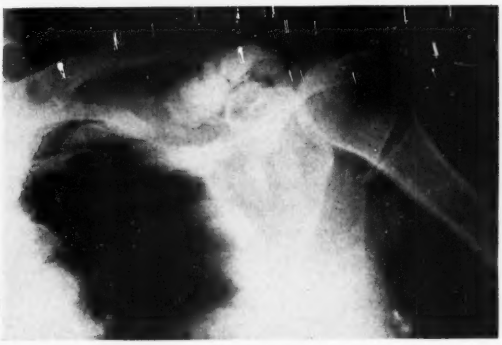

Fig. 4 (Case 2).—Roentgenogram of the left shoulder, showing the enlarged firm nodule next to the left clavicle.

Fig. 5 (Case 2).—Roentgenogram of right leg and hip, showing mass superior to right trochanter and calcification of femoral artery.

At this time the serum calcium was 11.5 mg.; serum phosphorus, 6.4 mg.; serum albumin, 5.2 gm.; serum globulin, 2.8 gm., and blood urea nitrogen, 43.4 mg. per 100 cc.

In November, 1952, the patent was hospitalized at the Illinois Research Educational Hospitals for a diagnostic workup. Chief complaints at this time were frequent paroxysms of coughing which often ended in vomiting, urinary frequency, pains in the shoulders and hips, and a dry skin.

On examination the patient was a well-developed well-nourished white woman appearing to be about her stated age, of 65, and in no apparent acute pain or distress. The skin on the hands, forearms, and exposed parts of the neck appeared dry, loose, and wrinkled. Eye examination revealed incipient band-shaped keratitis of both eyes (calcification of Bowman's membrane). The bulbar conjunctivae in the inner palpebral area showed peculiar opaque plaques and flecks, some of which appeared continuous with corneal calcification. There were large opacities in the

Fig. 6 (Case 2).—Roentgenogram made in October, 1952, showing metastatic calcification involving both kidneys.

middle of each tympanic membrane, which were white and irregular in outline. The patient was edentulous and wore well-fitting dentures. On the postpharyngeal wall were several small pinhead-size yellow-white nodules. The tongue was flat, with fissuring. There was a soft systolic murmur, heard best at Erb's space; the second aortic sound was greater than the second pulmonic sound, and there were occasional premature beats. The abdomen was slightly tender throughout; no organs or masses were palpable. The patellar reflexes were hyperactive, and there was an unsustained ankle jerk clonus present bilaterally. Results of neurological examination were otherwise within normal limits. Blood pressure was 130/80.

Examination of the blood disclosed hemoglobin 12.5 gm. per 100 cc., a hematocrit level of 35%, red blood cell count of 4,000,000 per cubic millimeter, and white blood cell count of 8,000 per cubic millimeter, with 84% neutrophiles, 15% lymphocytes, and 1% monocytes. The urine had a specific gravity of 1.010, pH 7.0, a plus reaction for albumin, and a plus reaction for calcium (method of Sulkowitch). The electrocardiogram showed no abnormalities. The basal metabolic

rate was —2%. The urea clearance test was 4.8 cc. (standard, 41.0 cc.). On a Kepler-Power water test the specific gravity remained at 1.010 and the half-hour volumes varied between 2 and 70 cc. There was 25% excretion of phenolsulphonphthalein at 120 minutes. The Kahn test was negative. Other values were serum calcium 12.0 mg. per 100 cc.; urine calcium, on two occasions, 202 mg. per 24 hours, with a 1,417 cc. output, and 148 mg. per 24 hours, with a 680 cc. output. The calcium intake at this time was low, being 118.7 mg. per 24 hours. The insulin tolerance was found to be within normal limits, with blood glucose 118 mg. per 100 cc. at the start, 81 mg. one hour later, and 108 mg. two and one-half hours later, at the end of the test. Skin and muscle biopsies showed senile elastosis and normal muscle. An agglutination test for Brucella was negative. X-ray of the gastrointestinal tract revealed a markedly deformed and narrowed duodenal cap, probably secondary to an old duodenal ulcer. No crater was identified at this time. A calculation of the average calcium intake in food and medicine for the past 5 to 10 years was found to be approximately 800 mg. of calcium per 24 hours.

COMMENT

The clinical syndrome of the first patient, with widespread subcutaneous calcinosis, who died of uremia 10 days after admission, seems to belong to a definite entity. Recently at least eight such cases have been published.‖ All these patients took large amounts of milk, calcium, and alkali for their ulcers and ultimately developed several or all of the following signs or symptoms: elevation of serum calcium and phosphorus, metastatic calcinosis, band-shaped keratitis, hypocalciuria, mild alkalosis, and anemia, with normal alkaline phosphatase levels. If this syndrome is discovered in an early stage, the ultimate uremia can be prevented by cessation of milk and alkali ingestion.

One of us (I. S.) has seen at least five patients with ulcers of the stomach who were treated conservatively and who showed hypercalcemia. In these cases, too, the serum calcium returned to normal after milk was withdrawn. Therefore, in every ulcer patient who is treated conservatively the serum calcium should be tested frequently. When the serum calcium is high or when alkalosis develops, the diet should be changed in order to prevent calcinosis, not only in the subcutaneous tissues but also in the lungs, stomach, heart, and kidneys. Calcinosis of the kidney parenchyma is one of the major factors in the causation of uremia in this syndrome.

In those patients who take excessive amounts of milk, calcium, and alkali the calcium deposits are much more extensive than in the patients who suffer with hypercalcemia due to hyperparathyroidism. The danger of impairment of renal function is therefore greater in ulcer patients with faulty diet than in patients with hyperparathyroidism. It follows that the conservative treatment of ulcer patients may perhaps not be as dangerous as subtotal resection but that it nevertheless is not completely devoid of hazards.

The question has been raised of whether this syndrome develops especially in patients whose kidneys have been damaged before the milk diet and alkali administration has been started.

No preexisting renal disease was elicited in the history of our two patients. However, the presence of 4+ albuminuria and low specific gravity raised the question as to the possibility of preexisting pyelonephritis.

In this connection the interesting observations of Swyer and his associates [18] on hypercalcemia in patients with osteolytic skeletal metastases after androgen therapy should be mentioned. At autopsy such patients nearly always show signs of pre-

‖ References 6 and 20.

existing renal disease. In the same way, it seems possible that the calcinosis, hypercalcemia, and uremia are more likely to develop when patients with preexisting renal disease are treated with alkalis and/or a Sippy regime.

It is interesting to note that Becker and his associates found an incidence of 36% of renal parenchymal calcinosis in a review of 99 autopsy cases of chronic active or healed duodenal ulcer.[3] Sixty-eight per cent of these persons had a history of a high intake of absorbable alkalis. It was suggested by these authors that the renal parenchymal calcification was possibly due to both the large amounts of calcium in the diet and the transient asymptomatic episodes of alkalosis. In none of these cases was the involvement severe enough to cause renal failure.

It should be mentioned that the two cases presented here both show a slight increase in total serum protein. Case 1, however, demonstrated a reversal of the A/G ratio, which is at variance with that of the previously reported cases, in which increase seemed to be chiefly in the albumin. In Case 2 there was little elevation, demonstrating in the earlier values a reversal which may be indicative of renal damage; however, the latter figures were more nearly consistent with those published in previous cases.

SUMMARY

Two additional cases of metastatic calcification with dietary etiology are presented. The first accords well with the seven recently published cases. The second is rather unique in that the calcium intake was below recommended daily requirements, leaving the alkaline ash diet and excess alkali ingestion as the only observable dietary deviations. Thus it would appear that excess alkalinizing agents is the more important factor in the growing series of cases of pathological calcification due to diet.

Dr. Norman Van Wezel, of Foley, Ala., and Drs. Buford Hall and Harry Dowling, of the University of Illinois, assisted in the collection of information used in this paper.

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INCREASED CEREBROSPINAL FLUID PRESSURE AND PAPILLEDEMA IN MALIGNANT HYPERTENSION

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CUSHING and Bordley,[1] in 1908, observed a patient with high diastolic blood pressure, elevated cerebrospinal fluid pressure, and bilateral papilledema, whose papilledema was relieved by subtemporal decompression. Larsson, in 1923,[2] described 11 patients with hypertension, mostly secondary to renal disease, all of whom had papilledema and elevated cerebrospinal fluid pressure. Shelburne, Blain, and O'Hare [3] surveyed 50 hypertensives and found that 19 of 21 with papilledema had elevated cerebrospinal fluid pressure. Pickering,[4] after studying 34 hypertensives, in 1934, stated that any individual patient's cerebrospinal fluid pressure is relatively constant and that there is a close correlation between increased cerebrospinal fluid pressure and papilledema. He reaffirmed the latter view in 1952 [5] and suggested that high diastolic blood pressure causes high intrathecal pressure and this in turn, the papilledema, which characterizes the syndrome of malignant hypertension.

This explanation of the papilledema of hypertensive disease is not universally accepted. Fishberg and Oppenheimer,[6] in 1930, commented that they had repeatedly observed normal cerebrospinal fluid pressure (CSFP) in hypertensive patients with severe papilledema. Duke-Elder [7] stated that elevated CSFP is not a constant finding in the papilledema of hypertension; he considered it to be a collateral finding, which had no direct causal association with the level of arterial pressure. Leinfelder,[8] in 1950, citing work in progress, stated that marked edema of optic nerves of hypertensive patients often occurred while intrathecal pressure was normal.

The present study was undertaken to resolve these views by accumulating data from a large number of patients with and without papilledema.

METHODS OF STUDY

More than 400 measurements of cerebrospinal fluid pressure were made on 200 patients. One hundred had essential hypertension without papilledema, and 100 showed the syndrome of malignant hypertension with papilledema. The degree of papilledema was estimated on a 1 to 4+ basis, as was previously described.[9] Among those without papilledema, there were 49 males and 51 females, with an average age of 43 years (range 19 to 65); in the group with papilledema, there were 66 males and 34 females; the average age was again 43 years (range 12 to 67).

Repeated measurements of CSFP were made in 20 patients; in 1 there were as many as 90. The CSFP was measured in the usual way, with a water manometer. The patients lay on the

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute.

edge of a hospital bed and after the lumbar puncture straightened the body in as relaxed a state as possible. In the event of unusual anxiety or muscular tension, secobarbital sodium (Seconal), 0.1 gm., was given 30 minutes before the observation. The average of two resting diastolic blood pressure readings, taken the morning and evening of the day the CSFP was determined, was recorded as the blood pressure to be correlated with CSFP. As suggested by Pickering, 250 mm. of water was taken as the upper limit of normal CSFP.

One patient developed papilledema while under observation, and another became rapidly worse, with an increase in papilledema from 2 to 4+. Five patients lost their papilledema while under treatment with bacterial pyrogens; papilledema recurred in two of these. Variations of cerebrospinal fluid pressure during the episodes were measured.

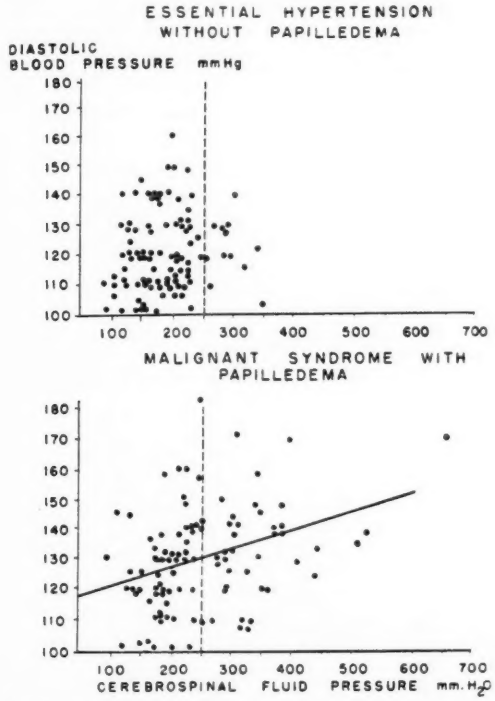

Fig. 1.—Relationship between cerebrospinal fluid pressure (CSFP) and diastolic arterial pressure in patients without papilledema (above), demonstrating no association of these functions, and in patients with papilledema (below), showing their association ($r = 0.35 \pm$; $r/SE_r = 3.5$). The line drawn through the points is from the calculated regression equation. The statistical methods are those described by Hill.[12]

The spinal fluid protein levels of 48 patients with essential hypertension and of 59 patients in the malignant phase of the disease were measured. The average values were, respectively, 39 mg. (range 19 to 67 mg.) and 43 mg. (range 27 to 102 mg.) per 100 cc. The concentrations exceeded the limit of 50 mg. per 100 cc. in two patients with essential hypertension and in three patients with papilledema. The values found in these were, respectively, 67 and 85 mg., and 67, 85, and 102 mg. These patients manifested increased CSF protein and had clinically active cerebrovascular disease.

The Ayala index was calculated in 58 patients with papilledema and in 38 with normal optic discs (Ayala index $= \frac{\text{cc. removed} \times \text{final CSFP}}{\text{initial CSFP}}$). A value of <4 was considered to indicate increased intracranial tissue volume, providing the CSFP was initially elevated.

RESULTS

CSFP and Diastolic Pressure.—Figure 1 shows graphically the relationship of diastolic arterial pressure to cerebrospinal fluid pressure observed in these 200 patients. Among those with essential hypertension without papilledema, the lack of correlation is apparent. In the group with papilledema, there is a significant statistical relationship. The correlation coefficient (r) is 0.347, and r/standard error of r is 3.5. This degree of association is much less than would be expected if CSFP and arterial pressure were causally related. Thus, some patients with diastolic pres-

TABLE 1.—*Distribution of Observed CSFP in Hypertensive Disease*

	Spinal Fluid Pressure, Mm. H_2O				
	100-199	200-249	250-299	300-349	350 and Over
Patients with essential hypertension without papilledema, No.....	61	26	9	2	2
Patients with hypertension with malignant syndrome and papilledema, No.....	36	21	17	12	14

TABLE 2.—*Relationship of CSFP to Degree of Papilledema*

During Recovery				During Development or Relapse			
Patient	Degree of Papilledema	CSFP, Mm. H_2O	Time, Wk.	Patient	Degree of Papilledema	CSFP, Mm. H_2O	Time, Wk.
2	3	190	..	1	0	220	..
	2	175	4		2	190	4
	0	165	6		3	200	8
4	3	245	..	3	2	180	..
	1	220	7		3	205	16
	0	155	11		4	150	20
	0	350	19				
				4	0	155	..
5	2	180	..		0	350	8
	0	195	4		1	210	15
					1	185	21
6	2	220	..				
	1	220	7	6	0	155	..
	0	155	14		2	400	6
7	3	145	..				
	2	124	6				
	0	210	12				

sures as high as 160 mm. Hg have CSFP less than 250 mm. H_2O; others had diastolic blood pressures of less than 110 mg. Hg, yet CSFP was greater than 300 mm. H_2O.

CSFP and Papilledema.—The distribution of CSFP in the two patient groups is further demonstrated in Table 1.

Fifty-seven of the 100 patients who had papilledema had normal CSFP; 87 of those without papilledema had CSFP of less than 250 mm. H_2O. Of those who had a CSFP greater than 350 mm. H_2O, 14 had papilledema and 2 did not.

The data of Table 1 demonstrate a loose association between papilledema and increased CSFP. That this association is subject to random variations which testify

against a causal relationship of increased CSFP to papilledema is further shown in Table 2, which presents observations among patients whose papilledema changed, remitted, or recurred. In these, the height of CSFP had no regular relationship to changes in papilledema.

Inconstancy of CSFP in Hypertensive Patients.—Figure 2 is the graphic record of measurements of CSFP made in a single patient at intervals of two to three days for a period of six months. He had Grade IV papilledema complicated by optic atrophy. Methods of available treatment did not control his disease, and he eventually died in uremia. CSFP varied from 50 to 450 mm. H_2O, without constant relationship to diastolic blood pressure.

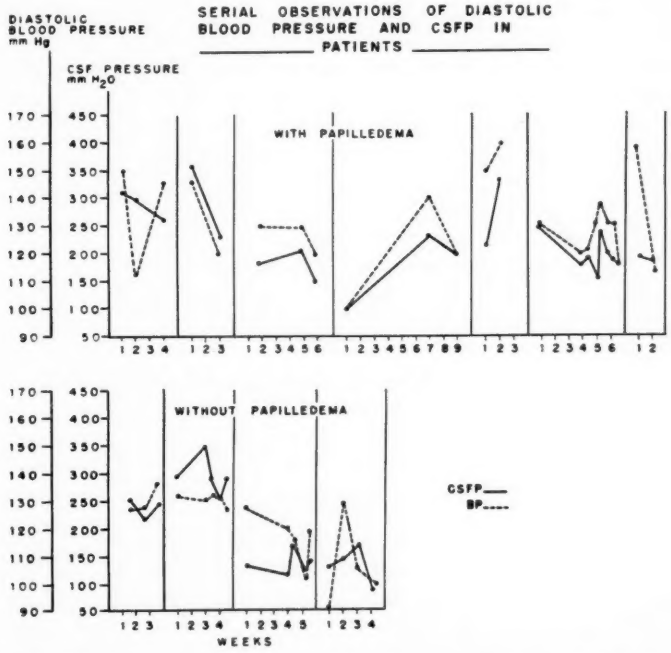

Fig. 2.—Serial observations of the association between diastolic arterial pressure and CSFP, made in one patient with papilledema and embodying 90 measurements over an interval of three months. No association of the two functions can be demonstrated in this case.

Figure 3 shows similar fluctuations of CSFP, taken at intervals of 1 to several weeks, among seven patients with papilledema and four without. Wide changes of CSFP were observed; an inconstant relationship to diastolic blood pressure seems to be demonstrable.

Ayala Index and CSFP.—The Ayala index is used as a relative measure of intracranial tissue volume; when CSFP is high, a low index (<4) would be evidence of increased brain volume, such as might result from cerebral edema, and a high index would indicate the presence of increased CSF volume. The average index in patients without papilledema was 6.1 (range 2.6 to 8.6); the index was less than 4 in three patients, none of whom showed increased CSFP. Among patients

with papilledema, the average index was 5.9 (range 1.9 to 9.4). Three patients in this group, whose index values were less than 4, had CSFP values of more than 300 mm. of water, one of them reaching 650 mm.; each of these died of cerebral hemorrhage within 48 hours after the observations were made. At the time the measurements were made, there was no paralysis and the CSF was clear; however, CSF protein was increased >50 mg. per 100 cc. The association of papilledema, high CSFP, a low Ayala index, and increased CSF protein seems to be worthy of further study as to its prognostic significance.

Thus, insofar as a low index with high CSFP indicates the presence of cerebral swelling, the data indicate that cerebral swelling is not a basic factor in the increased CSFP and papilledema sometimes observed in patients with severe hypertensive disease. The lack of association between the Ayala index and papilledema is further evidenced by calculations among 24 patients with increased CSFP; 10 of these showed papilledema, and 5 did not; the means of the indices in these two groups were identical, at 5.5.

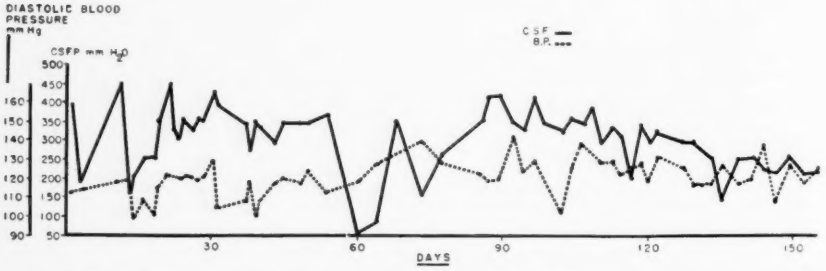

Fig. 3.—Serial observations, at intervals of weeks, of the association between diastolic arterial pressure and CSFP in seven patients with and four patients without papilledema.

COMMENT

As Pickering [4] has observed, the level of diastolic arterial pressure and the level of CSFP in hypertensive patients with papilledema show some correlation; no such association is demonstrable in hypertensive patients without papilledema and in patients with papilledema; the correlation between the two functions is not, as has been suggested, "close." The degree of association in this group is not sufficient to suggest that increased diastolic pressure is a direct cause of increased CSFP; thus, 13% of patients with hypertension but without papilledema had abnormally elevated CSFP; many patients with papilledema did not show elevated CSFP, and in those whose papilledema fluctuated, remitted, or recurred no association could be demonstrated between these changes and the level of CSFP.

Serial observations of CSFP in individual patients show rather wide fluctuations; the inconstancy of CSFP as compared with the relative constancy of arterial pressure may account for some of the looseness of the association between these functions. This supposition further diminishes the probability that increased diastolic pressure is a direct cause of increased CSFP.

Since it cannot be established that increased diastolic pressure causes increased CSFP, which in turn causes papilledema, it seems likely, as Duke-Elder [7] suggested, that the association between these functions is collateral rather than causal. In other

words, these are three more-or-less independent manifestations of severe hypertensive vascular disease. Until further data are forthcoming, it seems that papilledema as well as elevated CSFP must, like hypertensive encephalopathy, be regarded as examples of the unexplained neuropathies which are associated with severe hypertension.

The Ayala index, in the presence of increased CSFP, is widely accepted as an indication of the ratio between brain volume and volume of cerebrospinal fluid. Comparison by means of this index between patients with and those without papilledema indicates that papilledema is not associated with any evident increase in brain volume. Such might occur if papilledema were a function of generalized cerebral edema. Further, papilledema and increased CSFP cannot be attributed to increased cerebrospinal fluid volume.

While the increased CSFP of severe hypertension cannot be attributed to either increased brain or increased CSF volume, one further explanation remains. Rich, Scheinberg, and Belle [10] have recently shown that variations in cerebral blood flow cause parallel changes in CSFP and have attributed this association to the effect of variations in the volume of the intracerebral vasculature. Cerebral blood flow is not increased in patients with severe hypertension [11]; consequently, this cause of an increase in vascular volume cannot explain the high CSFP found in many patients with severe hypertension. If then brain volume, CSF volume, and cerebral blood flow are relatively normal in severe hypertension, increased CSFP can, by exclusion, be attributed to distention of cerebral vessels; such distention could result from the coincidence of severe arteriolar constriction, greatly increased arterial pressure, and weakened vascular walls; this explanation would account for such association as exists between increased CSFP, increased diastolic arterial pressure, and papilledema and other signs of severe hypertensive vascular disease.

SUMMARY

A study is reported of the association of cerebrospinal fluid pressure (CSFP), diastolic arterial pressure, and papilledema, based on more than 400 measurements of CSFP made in 200 patients with hypertensive disease, 100 of whom manifested papilledema.

No association between diastolic pressure and CSFP was found in hypertensive patients without papilledema; in hypertensive patients with papilledema the statistically significant correlation was not sufficient to indicate causation, since patients without papilledema showed elevated CSFP and patients with severely elevated diastolic pressures were often free of papilledema.

Similarly, in serial observations on patients whose papilledema altered in severity, remitted, or recurred, no close association between these changes and CSFP could be shown.

Serial observations of CSFP in individual patients show considerable fluctuations in this function, independent of diastolic pressure.

Papilledema and increased CSFP, like hypertensive encephalopathy, are to be regarded as specific manifestations of hypertensive disease, unrelated as cause and effect.

Observations of the Ayala index in these patients form the basis for a suggestion that the increased CSFP seen in hypertensive disease may result from distention of cerebral vessels.

Our present colleague, Dr. Harriet P. Dustan, and our former colleagues, Drs. Henry Fertig and Robert Birchall, gave assistance, and Mrs. Ruth Korenchan assisted in the statistical treatment of the data.

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EXSUFFLATION WITH NEGATIVE PRESSURE

Physiologic and Clinical Studies in Poliomyelitis, Bronchial Asthma, Pulmonary Emphysema, and Bronchiectasis

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OF THE various physical methods developed for eliminating bronchial secretions,* exsufflation with negative pressure (E. W. N. P.) was recently reported as the most effective.† The principle of E. W. N. P. depends on (1) gradual inflation of the lungs by a positive pressure of 30 to 40 mm. Hg; (2) a swift withdrawal of air from the fully expanded lungs at the beginning of expiration, utilizing a sudden pressure drop to 30 to 40 mm. Hg below the atmosphere; (3) explosive decompression produced by a 60 to 80 mm. Hg decrease in pressure in 0.02 seconds. The latter pressure drop would result in an instantaneous intrathoracic gas expansion of approximately 10% of the total lung capacity, or 400 to 500 cc. of air, if the suction blower provided an air velocity of this magnitude. E. W. N. P., therefore, includes effects of the two methods of mechanically eliminating bronchial secretions previously described, (*a*) exsufflation and (*b*) explosive decompression by means of the cough chamber.‡

In exsufflation alone, expiratory flow rates of the order of 60% of those of human coughing were produced by utilizing the elastic recoil of lungs previously expanded by a 40 mm. Hg pressure. In the cough chamber, a pressure drop of 100 mm. Hg in 0.06 seconds took place in the atmosphere surrounding the body but a differential pressure of 40 mm. Hg was applied to the chest by means of a close-fitting baffle surrounding the neck. The latter method utilized the rapid expansion of the intrathoracic gas by the pressure drop of 100 mm. Hg plus a chest compressing pressure of 40 mm. Hg to achieve an effect similar to the natural cough. The attainment by E. W. N. P. of expiratory flow rates surpassing those of a natural cough of normal subjects suggested the greater effectiveness of E. W. N. P. than the two previously described methods of mechanical coughing.[5] The experimental studies by Bickerman,[8] in which foreign bodies were blown from the lungs of dogs, confirmed this opinion.

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The purpose of this paper is to present the effect of E. W. N. P. as a therapeutic agent in patients with poliomyelitis and other neurological disorders, bronchial asthma, pulmonary emphysema, bronchiectasis, postoperative pneumonia, and pulmonary atelectasis.

METHODS

The technique of the use of E. W. N. P. has been described in detail elsewhere.[9] Briefly, a motor blower unit is used to produce a positive pressure of 30 to 40 mm. Hg gradually over a period of 2.5 seconds. The volume of air introduced into the respiratory tract by means of that pressure fully inflates the lungs. As soon as the peak inspiratory pressure is reached, a negative pressure of 30 to 60 mm. Hg is produced by either the same or a separate motor blower unit which sucks air from the respiratory tract at volume flow rates of 6,000 to 20,000 cc. per second, depending on the model of E. W. N. P. used. The intramask pressures of various types of E. W. N. P. were recorded by means of a pressure transducer-amplifying system on a direct-writing electrocardiograph (Sanborn Viso-Cardiette) (Fig. 1), and the corresponding ranges of expiratory volume flow rates were obtained. A hand-operated solenoid valve model § produced total pressure drop of 45 mm. Hg in 0.03 seconds, and the resulting expiratory volume flow rates were 6,000 to 7,000 cc. per second.

A hand-operated E. W. N. P. with a spring-type, nonelectrical valve,‖ with a pressure fall of 63 mm. Hg in 0.02 seconds, produced expiratory flow rates of 8,000 to 10,000 cc. per second.

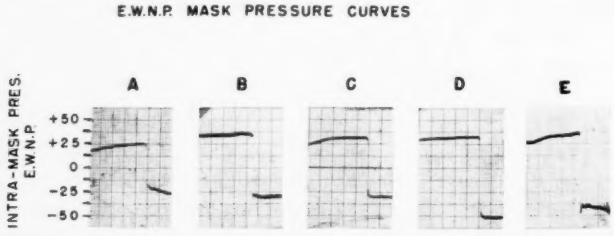

Fig. 1.—Mask pressure curves obtained with various types of E. W. N. P. revealed the following pressure changes: *A*, in the hand-operated solenoid-operated model the pressure falls from + 25 mm. Hg to — 20 mm. Hg in 0.03 seconds; *B*, in the automatic pressure controlled single-motor model the pressure falls from + 35 mm. Hg to — 35 mm. Hg in 0.02 seconds; *C*, in the hand-operated spring-type model a pressure drop occurs from + 33 mm. Hg to — 30 mm. Hg in 0.02 seconds; *D*, the two-motor automatic model has a pressure fall from + 32 mm. Hg to —48 mm. Hg in 0.02 seconds; *E*, in an automatic single motor type E. W. N. P. with increased pressure range produced by means of a Powerstat a fall in pressure from + 37 mm. Hg to — 46 mm. Hg takes place in less than 0.02 seconds.

An automatic two-motored model,¶ producing pressure drops of 80 mm. Hg or more in less than 0.02 seconds, had flow rates ranging between 8,000 and 20,000 cc. per second.

When a powerstat was used to boost the line voltage of the automatic single-motor E. W. N. P.# to 135 volts, pressure drops up to 81 mm. Hg were obtainable in 0.02 second and expiratory volume flow rates up to 15,000 cc. per second were achieved.

The duration of the negative pressure cycle is 2.0 seconds in the apparatus which is automatic in operation; the cycling rate, pressure, and volume settings are predetermined, but controls permit adjustments of these variables. Five to six exsufflations are repeated 6 to 10 times at intervals of one minute during each session of treatment. The courses of E. W. N. P. are generally given at one- to three-hour intervals. In most cases, and especially in the presence of bronchospasm, prior widening of the bronchial tree is achieved by the inhalation of 0.2 to

§ This type is manufactured by the Eliot Medical Plastics Co., Lynn, Mass.
‖ This model is made by O. E. M. Corporation, East Norwalk, Conn.
¶ This model is made by the O. E. M. Corporation, East Norwalk, Conn.
# This model is made by the O. E. M. Corporation, East Norwalk, Conn.

0.5 cc. of nebulized epinephrine, 2.25% racemic epinephrine, or 0.5% isopropyl epinephrine diluted with 2.0 cc. of isotonic sodium chloride solution.* The patient is instructed to inspire with the incoming stream of air which inflates the lungs and, when the negative pressure cycle begins, to exhale without either holding his breath or attempting to cough. Forcible coughing in patients with pulmonary emphysema might narrow the lumen of bronchi prematurely and diminish the expulsive action of the high volume flow rate from the lungs to the mouth.

The effect of E. W. N. P. on the vital capacity of patients with poliomyelitis, other neurological disorders, bronchial asthma, pulmonary emphysema, and bronchiectasis was determined by means of a McKesson-Scott Vitalometer, a Bennett vital capacity apparatus, or a Benedict-Roth Ventilometer. In one series of patients the immediate effect of the elimination of mucopurulent plugs from the tracheobronchial tree on the vital capacity was studied.

The patients were evaluated as to their clinical improvement, taking into account the presence or disappearance of atelectasis by x-ray films, the changes in vital capacity, and the effects of E. W. N. P. on bronchial secretions, including in one case direct inspection of the bronchial tree during an operation for lobectomy.

TABLE 1.—*Summary of Clinical Changes of 103 Patients with Obstructive Dyspnea Due to Retained Secretions, Following 106 Courses of E. W. N. P.*

Diagnosis and Complications	Courses of Treatment, No.		
	Unimproved	Improved	Total
Neurological conditions including poliomyelitis			
Atelectasis	1	11	12
Retained secretions	1	9	10
Postoperative state			
Atelectasis	0	4	4
Retained secretions	1	3	4
Bronchial asthma and chronic bronchitis			
Atelectasis	0	2	2
Retained secretions	2	20	22
Pulmonary emphysema			
Retained secretions	4	25	29
Bronchiectasis			
Atelectasis	1	1	2
Retained secretions	4	17	21
	14	92	106

CLINICAL RESULTS

A series of 103 patients with respiratory difficulties and retention of bronchial secretions was treated with 106 courses of E. W. N. P. The results of the complete series are summarized in Tables 1 and 2.

Fourteen patients suffering from a subacute or chronic phase of bulbar, spinal, or bulbospinal poliomyelitis received 17 courses of E. W. N. P. treatment. Of this group, six patients who had had pulmonary atelectasis once and one patient who had had this condition twice had been unsuccessfully treated prior to E. W. N. P. by measures which facilitated elimination of sputum, including suction by catheter through the oropharynx, positioning, and postural drainage. Three patients who had to be returned to the respirator could be removed from it within 48 hours of the start of E. W. N. P. treatment. In these seven patients pulmonary atelectasis cleared after the use of E. W. N. P.; roentgenographic aeration occurred

* An air pump is suitable for this purpose, the nebulizer being attached to the plastic tube adjoining the mask. The pump is manufactured by the Maihof Engineering Company, Avenel, N. J.

TABLE 2.—*Summary of Results of Treatment of Patients with Pulmonary Atelectasis, Using E. W. N P.*

	Primary Diagnosis	Condition Before Treatment	Duration of Treatment	Result of Treatment
1 (A. R.)	Spinal poliomyelitis	Upper respiratory infection 3 days, signs of atelectasis RLL 24 hr.	3 days q. 1 h.	RLL aerated in 12 hr.; atelectasis cleared in 24 hr.; elimition of purulent sputum
2 (F. L.)	Encephalobulbospinal poliomyelitis	Upper respiratory infection 2 days, signs of atelectasis LLL 12 hr.; returned to respirator	3 days q. ½ h.	LLL aerated in 12 hr.; atelectasis cleared in 30 hr.; elimination of up to 3 cm. plugs of purulent sputum; removed from respirator
3 (B. G.)	Spinal poliomyelitis	Upper respiratory infection 23 days, signs of atelectasis RLL, RML 9 days; returned to respirator	6 days q. ½ h.	RLL aerated in 48 hr.; RLL and RML atelectasis cleared in 6 days; elimination of up to 2 cm. hard plugs of sputum; removed from respirator
4 (C. D.)	Spinal poliomyelitis	Chronic sinusitis 1 mo., atelectasis segment RLL 48 hr.	2 days q. ½ h.	RLL aerated 24 hr.; elimination of mucopurulent sputum
5 (S. D.)	Spinal poliomyelitis	Upper respiratory infection 6 wk., atelectasis more than 3 days; atelectasis left lung	7 days q. 1 h.	Elimination of mucopurulent sputum; improvement of ventilation; atelectasis left lung cleared in 7 days
6 (H. W.)	Transverse section spine at C-6	Upper respiratory infection 2 wk., atelectasis 10 days ? left lung; returned to respirator, bronchoscopy before E. W. N. P.	3 days q. 2 h.	Atelectasis cleared in 70 hr.; elimination of mucopurulent secretions; removed from respirator
7 (R. B.)	Transverse section spine at C-4	Atelectasis LLL 48 hr.; tracheotomy, bronchoscopy before E. W. N. P., returned to respirator	2 days q. 1 h.	Atelectasis cleared in less than 12 hr.; elimination of purulent plugs and two blood clots 5 and 7 cm. long; removed from respirator
8 (D. B.)	Fractured ribs	Atelectasis left upper lobe 48 hr.; tracheotomy, bronchoscopy; sternal retraction	3 days q. 1 h.	Atelectasis cleared in 72 hr.; sternal retraction ceased in 6 hr.; markedly improved ventilation
9 (V. L.)	Postoperative salpingo-oophorectomy	Atelectasis RLL and LLL, dyspnea, no spontaneous coughing	2 days q. 1 h.	RLL and LLL aerated in 24 hr.; improved ventilation; atelectasis cleared in 48 hr.; elimination of mucopurulent secretions
10 (M. G.)	Exploratory laparotomy Bronchial asthma	Discoid atelectasis RLL and LLL, no spontaneous cough; chest pain, dyspnea	3 days	Elimination of mucopurulent secretions; atelectasis cleared within 24 hr.
11 (P. G.)	Bronchial asthma	Atelectasis RLL and RML 11 days	7 days q. 1 h.	RLL and RML aerated in 2 days; atelectasis cleared in 7 days
12 (F. M.)	Bronchiectasis	Atelectasis of lingula 1 mo.	5 days q. 3 h.	Aeration of lingula in 48 hr.
13 (L. C.)	Primary atypical pneumonia	Atelectasis RML 6 days or more	2 days q. 1 h.	Atelectasis cleared within 36 hr.
14 (G. L.)	Rheumatic heart disease Bronchiectasis	Atelectasis RLL 6 wk.	6 days q. 4 h.	No change in atelectasis; external compression of bronchus to RLL suspected
15 (S. G.)	Undiagnosed neurological disease at birth	Atelectasis right lung ? since birth (7-week-old infant)	2 days q. 3 h.	No change in atelectasis; discontinued because of technical difficulty
16 (M. L.)	Postoperative gastrojejunostomy	Atelectasis RLL, RML 72 hr.	3 days q. 3 h.	Elimination of purulent sputum; atelectasis cleared in 72 hr.
17 (M. V.)	Postoperative cholecystectomy	Atelectasis RLL, RML ? 48 hr.	3 days q. 2 h.	Atelectasis cleared in 48 hr.
18 (C. J.)	Poliomyelitis, returned to respirator	Atelectasis right lung 4 wk.; 2 bronchoscopies unsuccessful	5 days q. 2 h.	Atelectasis aerated after 22 hr., cleared completely after 4 days; large amounts of mucopurulent sputum; out of respirator
19 (M. F.)	Poliomyelitis	Atelectasis right lung, 3 days	3 days q. 2 h.	Atelectasis partially aerated after 30 exsufflations; complete clearing in 48 hr.; large amounts of mucopurulent sputum
20 (C. J.)	Poliomyelitis, returned to respirator	Atelectasis RML 2 days	2 days q. 2 h.	Atelectasis aerated after 19 hr.; cleared after 2 days; large amounts of mucopurulent sputum; out of respirator

within 1 to 48 hours, and complete disappearance of x-ray signs of inflammation was observed in one to seven days. The rapid aeration of a lung with atelectasis of four weeks' duration is shown in Figure 2. In seven patients with respiratory insufficiency secondary to poliomyelitis, accumulation in the respiratory tract of large

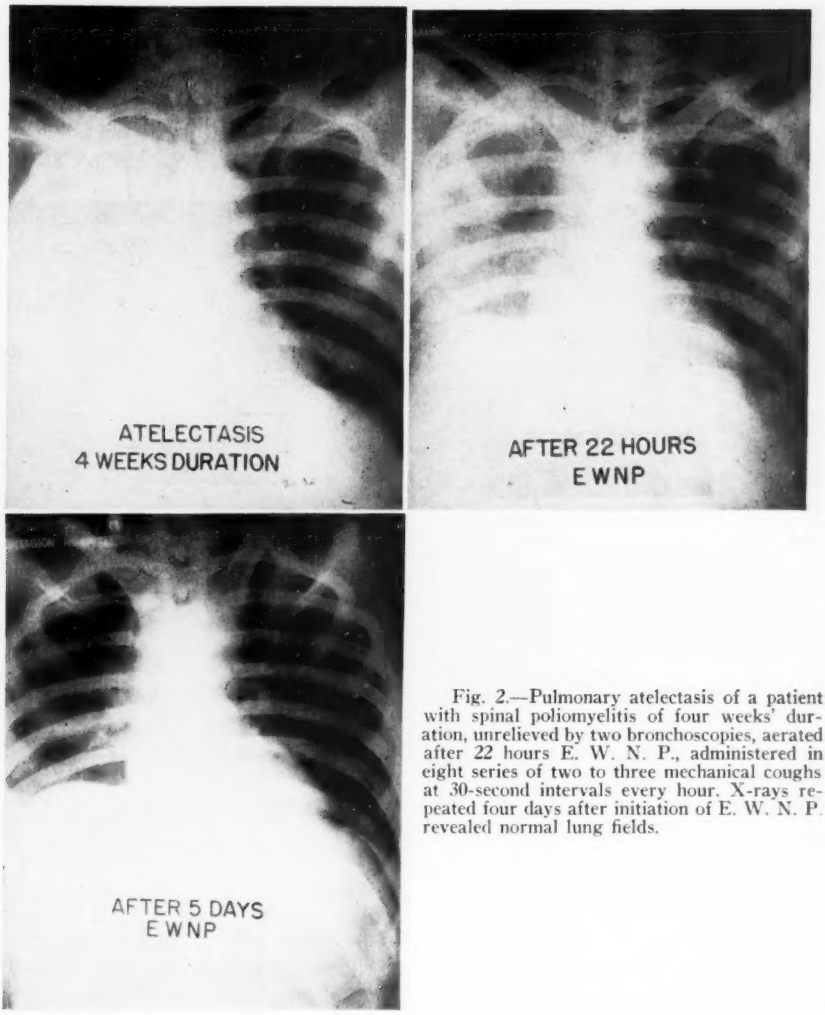

Fig. 2.—Pulmonary atelectasis of a patient with spinal poliomyelitis of four weeks' duration, unrelieved by two bronchoscopies, aerated after 22 hours E. W. N. P., administered in eight series of two to three mechanical coughs at 30-second intervals every hour. X-rays repeated four days after initiation of E. W. N. P. revealed normal lung fields.

amounts of mucopurulent secretions had resulted in severe dyspnea and cyanosis, unrelieved by bronchial suction, postural drainage, and positioning in all instances and, in two cases, by tracheotomy and suction. The use of E. W. N. P. resulted promptly in an outpouring of large amounts of mucopurulent sputum in six cases, with immediate relief of the symptoms of respiratory distress. These 13 patients

employ E. W. N. P. during upper respiratory infections to avoid recurrence of more serious chest complications. Prolonged use of E. W. N. P. by eight of these patients was followed by an increase in their average vital capacity of 55%.

In one patient with spinal poliomyelitis and bilateral lower lobe and right middle lobe pneumonia E. W. N. P. resulted in the production of large quantities of sputum. After a temporary improvement, with reduction in fever and improvement in ventilation, the patient's condition suddenly deteriorated. Death took place despite large doses of antibiotic, which did not control the infection, and frequent courses of E. W. N. P.

Atelectasis of one lobe of the lung in one patient and of the entire left lung in another patient, secondary to respiratory infections occurring in two cases of trans-

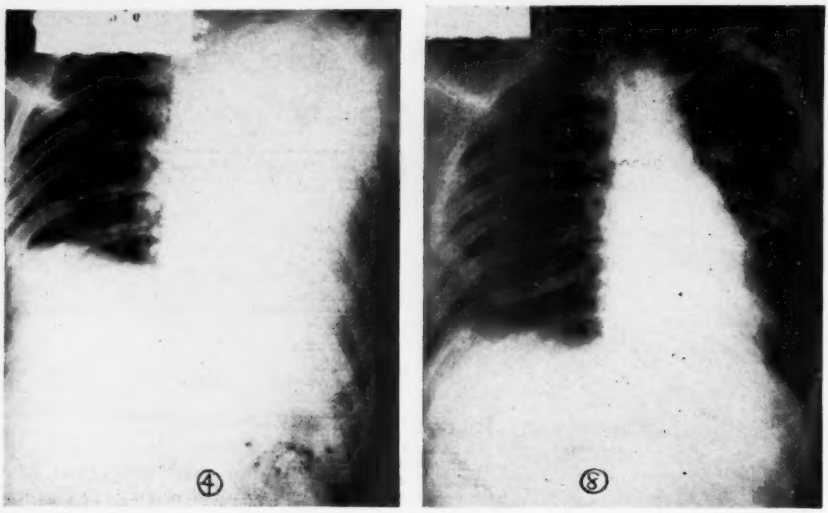

Fig. 3.—Pulmonary atelectasis in a patient with a transverse section of the spinal cord at the level of the sixth cervical vertebra, before E. W. N. P. and on the third day of treatment with E. W. N. P., when aeration of the left lung occurred.

verse section of the cervical spinal cord, were completely relieved of symptoms, with clearing of the radiographic evidence of pulmonary atelectasis in 24 and 70 hours, respectively (Fig. 3).

A severe paradoxical motion of the chest due to a partial atelectasis of the right lung was relieved for four hours after elimination of a large mucopurulent plug in a patient in whom tracheotomy with bronchial suction had been unsuccessfully used. Continued treatment with E. W. N. P. and other measures was followed by recovery.

A series of 76 patients with bronchopulmonary disease, including 24 with bronchial asthma, 29 with pulmonary emphysema, and 23 with bronchiectasis, were treated for dyspnea and retained bronchial secretions. Marked improvement immediately following E. W. N. P. was observed in 65 cases. In one patient with bronchial asthma, aeration of an area of pulmonary atelectasis occurred within 48 hours.

In another patient, with chronic bronchitis and an atypical pneumonia, an atelectasis of the right middle lobe was seen to be aerated within 36 hours following the first treatment with E. W. N. P. A third patient, with bronchiectasis and a right lower lobe atelectasis, manifested no clearing following a six-day course of E. W. N. P.; the cause of the lung lesion was obscure in this case, possibly due to external pressure on the right lower lobe bronchus. In another patient, with radiological non-aeration of the lingula of the lobe, marked clearing of the area occurred within 48 hours.

Lack of benefit from E. W. N. P. therapy in patients with bronchopulmonary disease appeared to be due, at least in part, to lack of cooperation of the patients and to inadequate experience in the correct application of mechanical coughing in the early part of the study. It was often found important to instruct the patient to breathe in slowly, i. e., permit air to enter the chest without holding the glottis closed, and then to breathe out slowly, permitting the rapid drop in negative pressure to expel sputum from the respiratory tract, rather than to attempt to aid the expiration induced by the machine by "coughing along with it."

Pulmonary atelectasis in a 7-week-old infant with neurological disease of undetermined origin was not cleared by a two-day course of E. W. N. P. given every three hours. Repeated bronchoscopies and bronchial suction by catheter also failed to clear the lesion, and the child died.

Mechanical coughing was used in four patients with postoperative atelectasis, with prompt aeration of the nonfunctioning areas. Disappearance of fever, relief of dyspnea, and production of large quantities of previously retained sputum occurred within 24 hours of institution of E. W. N. P. therapy in three postoperative patients whose course was complicated by retained secretions due to inability to cough. One patient with severe dyspnea due to accumulated secretions following an operation for a ruptured aneurysm of the aorta died on the third postoperative day of complications other than pulmonary ones.

The immediate effect of E. W. N. P. when used in conjunction with bronchodilator aerosols was studied in relation to the vital capacity in 67 patients with obstructive dyspnea; average increase of 15 and 42% in vital capacity over control levels took place in 12 patients with bronchial asthma and 34 cases of pulmonary emphysema, respectively. There was an increase in vital capacity of 39% in 10 patients with bronchiectasis and of 25% in 11 patients with neurological disorders. The effect of bronchodilator aerosols alone, tested in 54 cases prior to E. W. N. P., revealed increase in vital capacity of 9%, 36%, 27%, and 3% in patients with bronchial asthma, pulmonary emphysema, bronchiectasis, and neurological disorders, respectively. The small response to bronchodilator aerosols alone in this group of asthmatic patients seemed related to the presence of retained secretions and intractable bronchospasm. The comparison between the effects of bronchodilator aerosols with and without E. W. N. P. is shown in Figures 4 and 5 and Tables 3 and 4.

Studies of the vital capacities of 17 patients with obstructive dyspnea revealed an average increase in vital capacity of 55% in 8 patients with neurological disorders who were treated with E. W. N. P. for 30 days, of 24% in 5 patients with pulmonary emphysema receiving treatment for 7 days, and of 25% in 4 patients

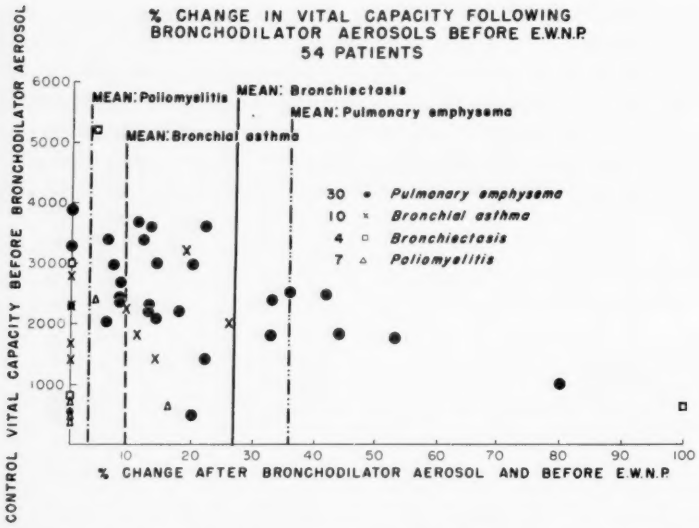

Fig. 4.—After the use of bronchodilator aerosols and before E. W. N. P. the mean vital capacities in 54 severely ill patients with pulmonary emphysema, bronchial asthma, bronchiectasis, and poliomyelitis were 9%, 36%, 27%, and 3% higher, respectively, than the control values.

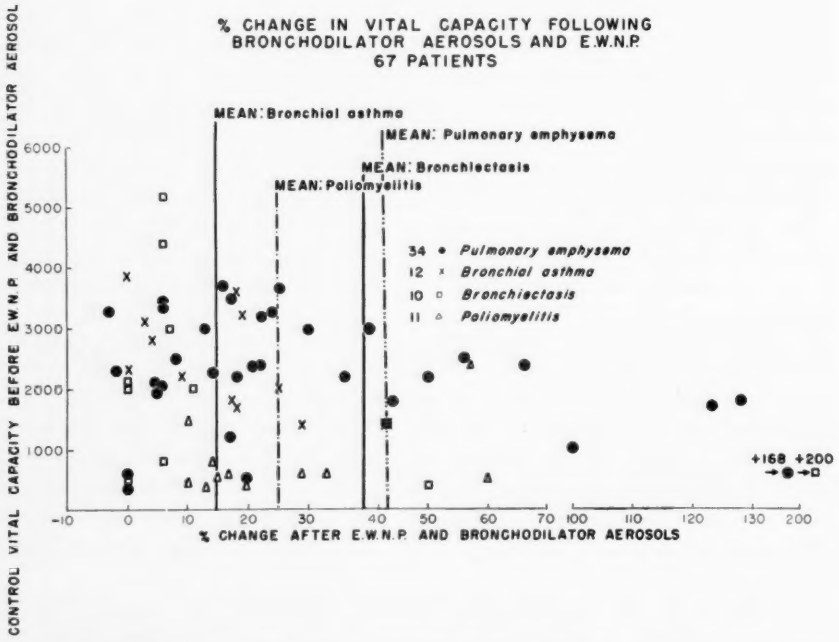

Fig. 5.—Mean vital capacities in 67 severely ill patients with pulmonary emphysema, bronchial asthma, bronchiectasis, and poliomyelitis were 42%, 15%, 39%, and 25% higher, respectively, after E. W. N. P. preceded by bronchodilator aerosols.

with bronchial asthma treated for 8 days. These long-term changes in vital capacity reflected clinical improvement which may have been related to other measures, although E. W. N. P. therapy was the new adjunct to the regimens.

In one patient with extensive bronchiectatic disease of the right upper lobe and slight involvement of the both lower lobes, E. W. N. P. was used just before lobectomy. When the main stem bronchus to the right upper lobe was opened at the time of operation, it was found to be free from purulent secretions. When the cylindrically dilated smaller bronchi of the right upper lobe specimen were opened, unusually small amounts of pus were found in them. The surgical procedure in this case appeared to be definitely facilitated by the preceding course of E. W. N. P.

TABLE 3.—*Percent Change in Vital Capacity of Patients Following the Administration of Bronchodilator Aerosols Alone and Combined with a Single Course of E. W. N. P.*

		Vital Capacity Before and After Bronchodilators Alone, % of Change*				Vital Capacity Before and After Bronchodilators with E. W. N. P., % of Change*		
Diagnosis	Total	−5 to +5	+5 to +20	+20 to +100	Total	−5 to +5	+5 to +20	+20 to +200
Bronchial asthma	10	5	4	1	12	4	5	3
Pulmonary emphysema	30	5	16	9	34	6	11	17
Bronchiectasis	4	3	..	1	10	3	5	2
Neurological disorders	7	6	1	..	11	..	7	4

* The figures in the columns indicate the number of tests.

TABLE 4.—*Mean Change in Vital Capacity Following Repeated Courses of E. W. N. P. in Seventeen Patients*

Diagnosis	Courses of E. W. N. P., No.	Average Duration of Courses, Days	Mean % Change from Control After E. W. N. P.
Neurological disorder	8	30	+55
Pulmonary emphysema	5	7	+24
Bronchial asthma	4	8	+25

The elimination of sputum before bronchography in one patient with bronchial asthma and another with bronchiectasis markedly improved the filling of the bronchi with radiopaque media. After the procedure the contrast substances were eliminated from the bronchial tree by 60 coughs with E. W. N. P. in each patient (Fig. 6). The patient with bronchiectasis who experienced signs of severe iodism within 24 hours of two previous bronchograms had no reaction following the elimination of iodized oil, U. S. P. (Lipiodol) by E. W. N. P.

The crucial therapeutic value of E. W. N. P. was manifested in a patient with bulbar poliomyelitis who was unable to raise retained secretions due to marked impairment in function of the thoracic musculature. The first instance of the use of E. W. N. P. was during acute respiratory distress due to bronchial plugging unrelieved by tracheotomy and subsequent tracheal and bronchial suction. Later, during an acute pulmonary infection and pulmonary atelectasis, E. W. N. P. appeared to be a lifesaving measure. Severe dyspnea required the use of the respirator with supplemental oxygen therapy by catheter. The pulse rate was 160 and the pulse was thready for 24 hours prior to E. W. N. P. Substantial clearing of the

area of pulmonary atelectasis in 12 hours took place coincident with elimination of large amounts of purulent sputum. Antibiotic therapy, with the use of polymixin B, was also of critical value in eliminating a pyocyaneous infection. The vital capacity was increased twofold, over a prolonged period of time, following repeated inflation of a nearly rigid thoracic cage as well as daily elimination of mucoid and salivary secretions by E. W. N. P. The use of a specially designed emphysema belt finally provided a surprising relief of respiratory effort, the respiratory rate and the minute volume of breathing being markedly reduced during periods of wearing the belt.

COMMENT

Exsufflation was previously defined as a method of producing high expiratory flow rates through the use of the elastic force resident in the fully distended lungs

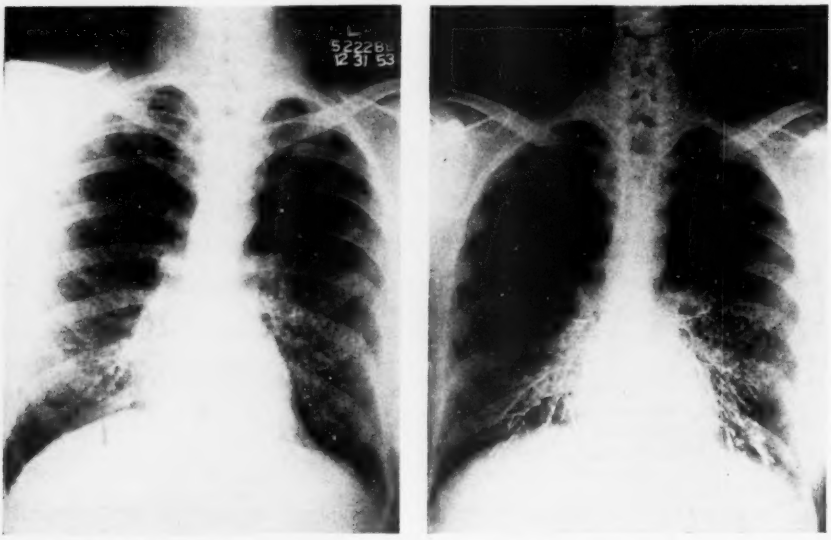

Fig. 6.—Elimination of radiopaque medium from the bronchial tree of a patient with bronchiectasis by 60 mechanical coughs with E. W. N. P. prevented severe iodism, which had complicated bronchography on two previous occasions. Left, bronchogram before E. W. N. P.; right, after 60 exsufflations with negative pressure.

and thorax; among the factors responsible for the physiological advantages of this form of supra-atmospheric intermittent pressure breathing were (1) a marked dilatation of the bronchial tree achieved by a 40 mm. Hg inspiratory pressure and (2) a swift termination of the peak inspiratory pressure. The addition of negative pressure at the start of the expiratory cycle resulted in flow rates of a far higher order of magnitude, capable, in fact, of therapeutic effects not achieved by exsufflation alone.

The high inspiratory pressure used in exsufflation, 30 to 40 mm. Hg, was not found to increase peripheral venous pressure, since expiration was terminated so quickly that the mean pressure of this type of ventilation was less than that ordi-

narily developed in the tank respirator.[2] The tidal volume generally obtained with this pressure, about 2,000 cc., was large enough to require only six respirations per minute to provide an adequate pulmonary ventilation.

Since exsufflation with negative pressure employs an inspiratory positive pressure of 30 to 40 mm. Hg followed by a subatmospheric (negative) pressure of at least 30 to 40 mm. Hg, the mean pressure obtained in this form of ventilation would be, manifestly, unusually low, depending on the length of the inspiratory as well as the expiratory phases. When the exsufflator was attached to the tank respirator, exsufflation was used for one-half hour, with an interval of one minute or two generally inserted at the end of each 10-minute period.† In treatment with the portable E. W. N. P. apparatus, with attachment to the face by a mask or special mouthpiece, 40 to 50 exsufflations are given but a rest is interposed after each five or six exsufflations in order to avoid hyperventilation. The mean pressure of E. W. N. P. is not of critical importance, since the duration of a single course of six coughing expirations is followed by one-half minute of normal breathing.

The increased effectiveness of E. W. N. P. over exsufflation, revealed by the experimental studies in which radiopaque mucin-thorium dioxide (Thorotrast) mixtures and foreign bodies were rapidly eliminated from the lungs of dogs,[8] may also be readily observed when a distensible rubber bag is substituted for the lungs and foreign bodies, such as steel and lead bullets, nails, tacks, and safety pins, are blown out of the plastic tube during the E. W. N. P. maneuver. A human cough of maximal effort does not move lead bullets from the same tube.

The therapeutic use of E. W. N. P. in neurological disorders, including poliomyelitis, can be considered applicable not only to seriously ill patients with pulmonary atelectasis but also to a large group of cases in which inadequate elimination of mucoid and salivary secretions has impaired respiratory function, resulting in varying degrees of increased breathing effort, anoxia, or the necessity for mechanical ventilation, with confinement to the tank respirator or the rocking bed.‡ With routine employment of exsufflation, respiratory function has improved in some cases to a degree that made it possible to terminate the use of the respirator and in other instances has permitted the rocking bed to be used in place of the respirator. In some cases expiratory flow rates of 6,000 to 7,000 cc. per second appeared to be adequate until the bronchial secretions became more viscous. However, higher flow rates, of the order of 9,000 to 10,000 cc. per second, appear to be consistently more effective in eliminating viscid bronchial secretions, especially in cases with bronchospasm, when bronchodilator aerosols are also employed prior to each treatment.

In patients with bronchopulmonary infection E. W. N. P. is now used to provide bronchial drainage, in the hope that antibiotic therapy will be more effective, especially with smaller drug dosage.

The ability to produce an effective cough is impaired in patients with pulmonary emphysema because of the lessened elasticity of the lungs, among other factors, which together result in the intra-alveolar pressure becoming higher than the intrabronchial pressure, with retarded air flows during forceful expiration and cough.§

† The exsufflator attachment to the tank respirator is made by the De Florez Company, 116 E. 30th St., New York.

‡ References 7, 12, 13, and 15-17.

§ References 10 and 11.

Inadequate elimination of retained mucus is facilitated by the continuous inhalation of nebulized bronchodilator substances, prior to E. W. N. P. Although intermittent pressure breathing apparatus have been used to promote better aeration of previously unventilated alveoli and increased penetration of bronchodilator aerosols, the expiratory phase is, in our opinion, too slow to be in itself of any physical value in eliminating mucoid or mucopurulent secretions. As shown in our studies, prior nebulization of bronchodilator aerosols was of decided value in the clinical use of E. W. N. P., and comparative studies suggested a higher effectiveness in the elimination of mucopurulent material as a result of use of nebulized bronchodilator aerosols and E. W. N. P. than in the results of nebulized bronchodilator aerosols without E. W. N. P. This finding, clinically evident repeatedly, was borne out by the vital capacity determinations reported.

In previous reports on exsufflation, the additional value of adding manual compression of the chest was described as similar to the application of negative pressure in the dome of the respirator.‖ When 0.5 to 0.8 cc. of a bronchodilator solution, such as 1% epinephrine or 2.25% racemic epinephrine, is mixed with 2.0 cc. of isotonic sodium chloride solution and nebulized continuously, the relief of bronchospasm is apt to be considerable. Following this procedure with vigorous abrupt compression of the lower thorax and upper abdomen during the latter half of the expiratory cycle is, at times, followed by expectoration of mucus and relief of dyspnea comparable to that obtained by E. W. N. P. used after inhalation of bronchodilator aerosols. A clinical response of this kind is illustrated by records of the pulmonary ventilation in a recently treated patient with pulmonary emphysema (Fig. 7). It will be observed that the minute volume of breathing was 13,400 cc. during inhalation of room air and 7,950 cc. during inhalation of 100% oxygen prior to treatment. Fifteen minutes after treatment, the pulmonary ventilation was 8,560 cc. with air and 7,480 cc. with 100% oxygen. The decrease in breathing requirement was indicated by the much smaller difference between the ventilation with 100% oxygen and that with air. A similar situation is frequent in patients with bulbar poliomyelitis, in whom inability to swallow as well as to cough results in salivary and bronchial secretions dripping into the smaller bronchi, increasing resistance of the respiratory passageway and producing variable degrees of focal or lobar atelectasis, edema, infection, and increased respiratory effort. In patients with borderline hypoventilation, elimination of these secretions may well become a critical factor which will enable some of them to dispense with respirator treatment, tracheotomy, and bronchoscopic aspiration.

The value of exsufflation in the treatment of respiratory acidosis depends on the high tidal volume and minute volume of breathing produced by inspiratory pressures of 40 mm. Hg.¶ Intermittent pressure breathing accomplished by the tank respirator may result in the blowing off of CO_2,[14] but patients may breathe against the cycle of the respirator and show either no improvement or a decrease in ventilation.[13] The reason for this is that the pressures available in the conventional respirator are not high enough to force the patient necessarily to breathe with the inspiratory and expiratory cycles, as is accomplished with exsufflation and, especially, with exsufflation with negative pressure. The latter principle of treatment

‖ References 4 and 5.

¶ References 12 and 13.

would appear to be more effective in providing a swift elimination of carbon dioxide from the lungs, without the development of increased mean ventilatory pressures that embarrass cardiac output.

In the technical use of E. W. N. P., the ordinary mouthpiece is not serviceable unless a circular metal tube extends about 1 in. (2.5 cm.) within the mouth to depress the tongue, because otherwise the tongue may be sucked into the mouthpiece and stop the expiratory flow of air. A rigid tube within the mouthpiece covering part of the tongue is preferred by some patients, and the mask is preferred by others.[9]

The clinical benefit reported as a result of exsufflation and exsufflation with negative pressure appeared to be directly associated with the elimination of previously retained mucus or mucopurulent sputum.# Since the therapeutic value of

IMMEDIATE EFFECT OF TREATMENT WITH NEBULIZED EPINEPHRINE AND MANUAL COMPRESSION OF CHEST ON PULMONARY VENTILATION OF A PATIENT WITH PULMONARY EMPHYSEMA

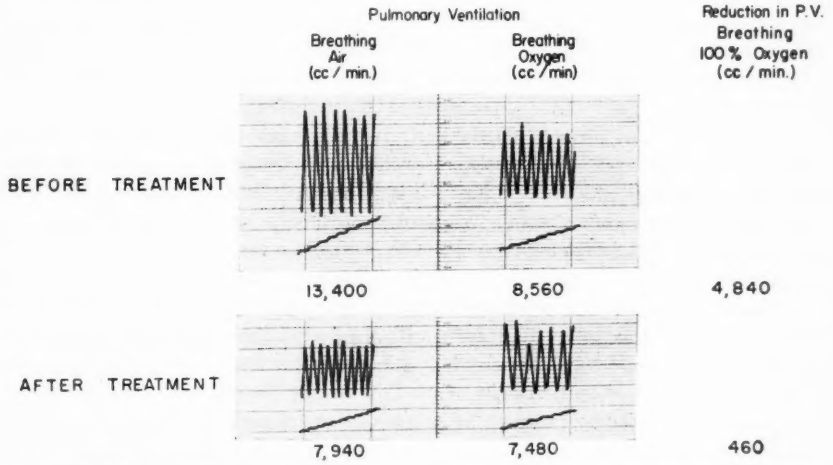

Fig. 7.—Manual (positive) pressure to the chest after the bronchi have been dilated reduces overinflation of the lungs in a patient with pulmonary emphysema; the pulmonary ventilation, with the patient breathing air, is decreased and is more nearly similar to that produced by breathing 100% oxygen.

these measures was dependent on the degree to which bronchial secretions impaired respiratory function, either in the production of obstructive dyspnea or in the promotion of pulmonary atelectasis and infection, E. W. N. P. is not proposed as a treatment for bronchial asthma, pulmonary emphysema, or poliomyelitis but simply as a mechanism of accomplishing drainage in patients whose respiratory difficulties are traceable to inadequate removal of secretions from the tracheobronchial tree.

In cases in which serious cardiorespiratory insufficiency was the result of occlusion of small bronchi, the successful evacuation of the offending mucopurulent sputum initiated a conspicuous relief of symptoms, with at times an apparently lifesaving result. However, in cases of chronic respiratory disease in which broncho-

References 7 and 15-17.

spasm was a more influential factor than retention of secretions, the use of E. W. N. P. was followed by little or no benefit. In some patients it was difficult to determine whether a harassing cough was due to bronchospasm or inability to expectorate mucus adherent to the bronchial wall. The procedure of therapeutic trial with bronchodilator aerosols followed by E. W. N. P. frequently was of help in determining whether or not retained mucus was the critical factor in the production of dyspnea.

The value of increased intra-abdominal pressure, accomplished by the head-down position or emphysema belts and sand-bag jackets applied to the lower abdomen, has been observed by us not only in patients with pulmonary emphysema but also in some cases of poliomyelitis.* Even if a slight degree of diaphragmatic motion can be initiated in these patients, the routine use of abdominal weights and abdominal breathing exercises may develop the remaining diaphragmatic muscle so that it can contract against increasing counterpressure applied to the abdomen and in this way augment ventilation of the lower lobes of the lungs. The importance of these measures for aiding diaphragmatic breathing has been stressed as a means of relieving dyspnea, but it has become more evident that diaphragmatic breathing aids the effectiveness of the cough by increasing the aeration of alveoli distal to bronchial mucus plugs, especially at the bases of the lungs, where secretions tend to stagnate.

Although a new physical method of treatment has been emphasized in this report, other measures of promoting bronchial drainage have been effective in the management of patients with poliomyelitis and allied breathing difficulties; these measures include bronchoscopic and post-tracheotomy suction and inhalation of wetting agents and bronchodilator aerosols, with or without intermittent pressure breathing.†

Failure to accomplish effective elimination of retained secretions may result from inability of the patient to breathe with the cycle of the apparatus. Cooperation of the conscious patient is required to achieve full inflation of the lungs during inspiration as well as high velocity of air flow during the expiratory phase. Hyperventilation is avoided by limiting the number of exsufflations to five or six, with an interval of one half to one minute between courses of treatment. Although rupture of an emphysematous bleb might take place as a result of distention of alveoli, no adverse effect of this or any other nature has been encountered in over 2,000 courses of treatment, including the results of exsufflation as well as those of E. W. N. P.

In one deeply comatose patient with cerebral hemorrhage, purpura, and bleeding from the lungs, exsufflation with negative pressure was followed by elimination of blood and mucus from the respiratory tract and clearing of the gurgling noise in the chest. After the last course of E. W. N. P., gastric contents were found in the mouth and the procedure was discontinued. The patient had been moribund, with a pulse rate of 160 and a respiratory rate of 6, and death ultimately took place. Although there was no evidence that aspiration of gastric content into the lungs occurred, the possibility of this complication should be kept in mind in cases in which the cardiac end of the stomach has lost its sphincter control. In current studies of Williams and Holaday,[28] in which E. W. N. P. was used on deeply

* References 7, 18, and 19.

† References 20-27.

anesthetized patients immediately after operation, no instance of aspiration of gastric contents from the stomach was found, nor were similar findings evident in the experimental studies of anesthetized dogs by Bickerman.[8] Nevertheless, it should be recognized that the pressures employed in E. W. N. P. are two to three times those previously used in inhalational therapy. Although relatively high velocity of air movement and elimination of mucoid and mucopurulent secretions have been frequently observed as a consequence of pressures of + and — 20 mm. Hg, the absence of adverse reactions and the increased effectiveness of the higher pressures employed have encouraged us to use E. W. N. P. as outlined. In a few cases of pulmonary emphysema in which mucus was apparently delivered from the smaller bronchi into the larger bronchi or trachea a sensation of suffocation has been temporarily experienced by the patient until he was able to cough up large plugs lodged in the upper respiratory tract. In these instances, a pressure of + and — 20 mm. Hg has been for a time adopted, in the attempt to promote a more gradual clearing of the respiratory tract.

A sensation of abdominal distention, followed by borborygmus, is a not infrequent finding during the initial courses of E. W. N. P. on new patients. If the inspiratory air volume supplied to the patient is too large, air may be swallowed and accumulates in the stomach. Diminution of the inspiratory volume completely abolishes this unpleasant side-reaction. In nearly all cases of pulmonary atelectasis occurring in patients with neurological disorders blood-streaked sputum has been observed during the first courses of coughs with E. W. N. P. Treatment has been continued when this occurs, since the blood apparently originates from the sites of detachment of mucus plugs from the bronchial walls. Immediately following the initial elimination of blood-streaked sputum, a profuse outpouring of mucoid or mucopurulent sputum occurs, indicating that the obstruction of the atelectatic area has been relieved. The elimination of tenacious sputum before and of contrast medium after bronchography in patients with bronchial asthma and bronchiectasis by means of E. W. N. P. is a useful method designed to improve the results of bronchography.

SUMMARY

Exsufflation with negative pressure (E. W. N. P.) has been used in a variety of clinical disorders characterized by retention of bronchial secretions and a resultant impairment of respiratory function. The principle of this mechanical method of eliminating mucus or mucopurulent sputum depends on a marked inflation of the lungs and bronchial tree by an inspiratory pressure of 30 to 40 mm. Hg followed by a rapid drop in pressure to 35 to 40 mm. Hg or more below atmospheric pressure. The total pressure drop, of 65 to 80 mm. Hg in a period of approximately 0.02 seconds, results in expiratory flow rates of a sufficiently high order of magnitude to blow secretions from the lungs. Expiratory flow rates, of 10,000 cc. per second, produced by a high-speed motor blower unit, are frequently two to five times higher than those obtained in coughs of maximal effort in patients with respiratory difficulties.

The clinical use of E. W. N. P. in cases of poliomyelitis and other neurological diseases with breathing difficulties appeared to be of critical value in 20 of 22 patients and responsible for the clearing of pulmonary atelectasis in 11, for removal from the respirator in 4, and for marked relief of obstructive breathing in all 20.

Marked benefit was also observed in seven patients in whom bronchoscopic suction or tracheotomy followed by suction by catheter had previously proved ineffective.

Clinical improvement of significant extent, manifested by relief of dyspnea and cough, was observed in 22 cases of branchial asthma and 43 cases of pulmonary emphysema and bronchiectasis. Postoperative pulmonary atelectasis cleared after treatment with E. W. N. P. in four cases. The elimination of retained mucopurulent sputum by means of E. W. N. P. was, at times, an effective method of relieving obstructive dyspnea, and, in cases in which accumulation of bronchial secretions appeared to maintain bronchopulmonary infection, this technique seemed to aid the management of respiratory infection by promoting a more efficient bronchial drainage than the patient himself was able to provide.

The vital capacity of 12 patients with bronchial asthma increased 15%, that of 34 patients with pulmonary emphysema increased 42% ; that of 4 patients with bronchiectasis increased 39%, and that of 4 patients with neurological disorders increased 25% after one treatment with E. W. N. P. and bronchodilator aerosols. Repeated courses of E. W. N. P. resulted in a mean rise in vital capacity of 55% in eight patients with neurological disorders and of 24% in nine patients with pulmonary emphysema and bronchial asthma.

The use of E. W. N. P. in patients with bronchial asthma and pulmonary emphysema, in whom retention of secretions played a less important role than bronchospasm, was accompanied by little or no benefit. The clinical indications for the use of this procedure depend on whether or not functional pathology is produced by inadequate elimination of mucus or mucopurulent sputum from the respiratory tract.

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SOLITARY CIRCUMSCRIBED LESIONS OF LUNG

Selection of Cases for Diagnostic Thoracotomy

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THE PERSON who has a solitary circumscribed lesion in the lung presents a difficult diagnostic problem. In military personnel such nodules are often found on routine roentgenograms of the chest made incident to administrative physical examinations or in persons hospitalized for some unrelated condition. Many of these so-called "coin" lesions have been found in civilian practice during mass roentgenographic surveys for tuberculosis.

From a review of over 714 histologically proved cases reported it is evident that about 80% of these nodular infiltrates represent a serious disease process (Table 1). Malignant tumors make up 35% of the total, and, of these, three-fourths are primary bronchogenic carcinomas; one-eighth are metastatic tumors; one-tenth are bronchial adenomas (5 to 10% eventually metastasize), and the remainder are sarcomas of various types. Forty per cent of the total are inflammatory lesions, many of which may be dangerous foci of tuberculosis. Of the remaining heterogeneous lesions, some are of questionable innocuousness.

Ordinarily clinical investigation, including history, physical examination, roentgenograms of the chest, bronchoscopy, culture and cytological examination of the sputum, skin testing, and other procedures, has yielded few positive diagnoses. The recent trend towards early resection of all such undiagnosed pulmonary lesions has come about mainly through fear of primary bronchogenic carcinoma and hope for its theoretic cure or because of the unpredictable nature of many inflammatory lesions.*

The risk attendant to surgical removal of an undiagnosed round pulmonary infiltrate must be compared with the likelihood that one of the above conditions is present. In this regard two factors appear to merit consideration, (1) the age of the patient and (2) whether or not the lesion is calcified.

AGE FACTOR

Some investigators feel that the use of the age factor as a guide to the diagnosis of carcinoma of the lung is proving somewhat unreliable, since such malignant tumors are now being recognized in younger persons.† There seems to be little doubt, however, that advancing age predisposes to lesions of a malignant nature. Condon [9] found a 63% incidence of malignancy in isolated round lesions of the

* References 1, 2, 4, 5, 7, and 16.
† References 7 and 21.

TABLE 1.—*714 Histologically Proved Cases of Isolated Circumscribed Lesions of the Lung*

	Bernatz & Claggett [1]	Hood & Others [2]	Grow & Others [3]	Davis & Klepser [4]	Sharp & Kinsella [5]	Husfeldt & Carlsen [6]	Wolpau [7]	Effler & Others [8]	Condon [9]	Effler [10]	O'Brien & Others [11]	Abeles & Ehrlich [12]	Total	Percentage
Total cases in series	180	156	86	71	54	33	25	24	27	16	21	21	714	100.0
Malignant tumors	61	55	21	37	17	8	10	4	18	7	9	8	225	35.8
Primary bronchogenic cancer	54	25	20	33	11	4	6	1	17	6	8	5	190	26.6
Bronchial adenoma	7	12	..	..	2	1	2	..	..	..	..	1	25	3.5
Sarcoma	..	1	..	..	..	1	..	..	1	..	1	1	5	0.7
Neurogenic sarcoma	..	..	..	1	..	..	..	..	..	..	..	..	1	0.1
Lymphosarcoma	..	..	..	..	1	..	..	1	..	..	..	..	2	0.2
Neurofibrosarcoma	..	..	..	..	..	..	..	1	..	..	..	..	1	0.1
Lymphoblastoma	..	..	..	1	..	..	..	..	..	..	..	..	1	0.1
Metastatic malignant condition	..	17	1	2	3	2	2	1	..	1	..	1	30	4.2
Benign tumors	12	39	1	9	8	13	3	3	5	1	1	3	89	12.5
Hamartomas	12	25	1	..	5	6	2	1	4	1	..	..	57	8.0
Fibroma	..	..	..	5	2	..	1	1	..	..	..	1	10	1.4
Chondroma	..	..	..	2	1	..	..	..	..	..	1	1	5	0.7
Mesothelioma	..	3	..	..	..	..	..	..	..	..	..	..	3	0.4
Thymoma	..	1	..	..	..	..	..	..	1	..	..	1	3	0.4
Hemangioma	..	1	..	..	..	1	..	1	..	..	..	..	3	0.4
Dermoid cyst	..	..	..	..	..	3	..	..	..	..	..	..	3	0.4
Intercostal neuroma	..	..	..	..	..	3	..	..	..	..	..	..	3	0.4
Unclassified	..	..	..	2	..	..	..	..	..	..	..	..	2	0.2
Inflammatory lesions	77	67	45	23	21	3	10	9	2	8	10	9	284	40.0
Round foci of tuberculosis	..	..	37	17	11	2	7	7	2	8	8	5	104	14.6
Granuloma, undetermined type	65	65	..	1	..	..	3	1	..	..	..	..	135	19.0
Coccidioidal granuloma	..	..	3	..	..	..	..	..	..	..	..	..	3	0.4
Chronic pneumonitis	12	1	..	5	10	..	..	..	..	..	..	..	28	3.9
Chronic abscess	..	1	..	..	..	1	..	..	..	..	2	2	6	0.84
Empyema	..	..	3	..	..	..	..	..	..	..	..	..	3	0.40
Actinomycosis	..	..	1	..	..	..	..	..	..	..	..	..	1	0.1
Echinococcus cyst	..	..	1	..	..	..	..	1	..	..	..	..	2	0.2
Lipoid pneumonia	..	..	..	..	..	..	..	..	..	..	..	1	1	0.1
Bronchiectatic cyst	..	..	..	..	..	..	..	..	..	..	..	1	1	0.1
Miscellaneous	30	4	19	2	8	9	2	8	2	..	1	1	86	12.5
Bronchial cyst	..	4	13	2	8	4	..	6	1	..	1	..	39	5.5
Unclassified	25	..	..	..	..	..	..	..	..	..	..	..	25	3.5
A-V aneurysm	..	..	1	..	..	..	1	..	..	..	..	..	2	0.2
Pericardial cyst	..	..	..	..	..	..	1	..	..	..	..	1	2	0.2
Broncholithiasis	5	..	..	..	..	..	..	..	..	..	..	..	5	0.7
Diaphragmatic hernia	..	..	3	..	..	2	..	2	..	..	..	..	7	1.0
Liver abscess	..	..	2	..	..	..	..	..	..	..	..	..	2	0.2
Aortic aneurysm	..	..	..	..	..	1	..	..	..	..	..	..	1	0.1
Mediastinal cyst	..	..	..	..	..	1	..	..	..	..	..	..	1	0.1
Gastric cyst	..	..	..	..	..	1	..	..	..	..	..	..	1	0.1
Hematoma	..	..	..	..	..	..	..	..	1	..	..	..	1	0.1

lung in 27 patients over the age of 50. Davis and Klepser [4] reported a 70% malignancy rate in 40 consecutive elderly patients, and Effler [10] reported a rate of 44% in patients whose average age was 51.

The incidence of malignant tumors which appear as circumscribed round pulmonary infiltrates in persons under the age of 35 has not been adequately evaluated, since insufficient age-specific data have been included in most published series. This is especially true of bronchogenic carcinoma. O'Brien, Tuttle, and Ferkaney [11] reported 2 instances of primary bronchogenic carcinoma in persons 35 years of age or less from a series of 21 patients. Their experience seems unique in comparison with other published studies, however (Table 2). Hood, Good, Clagett, and McDonald,[2] in a much larger group, of 156 patients, at the Mayo Clinic, reported no instance of bronchogenic carcinoma in persons under 35. It is interesting to note that 96% of the 25 malignant conditions found were in persons over the age of 40. Mitchell [22] reviewed four series of patients with round lesions, reported from tuberculosis centers, in which the average age of patients was below 30 and stated that no

TABLE 2.—*Relationship of Age to Malignancy in Circumscribed Nodular Lesions of the Lung*

Series	Total Cases	Age Range, Yr.	Average Age, Yr.	% Malignant	Primary Bronchogenic Carcinoma	Bronchogenic Carcinoma Under Age 35
Jones & Cleve	14	21-63	32	7	7	0
Mahon & Forsee [14]	55	18-63	..	7	3.6	0
Effler & others [8]	24	19-57	35	15	4.2	0
Husfeldt & Carlsen [6]	33	<35 to >35	>35	21	..	0
Hood & others [2]	156	6-67	..	35.5	16	0
Effler [10]	16	28-66	51	43.8	37	0
O'Brien & others [11]	21	.....	..	45	88.1	1
Davis & Klepser [4] *	71	25-74	49.5	55	46.5	0
Condon [9]	27	>50	>50	63	..	..
Davis & Klepser [4] †	40	"Older age group"	..	70	..	..

* Entire series.
† First 40 consecutive cases of their series—all patients in older age group, exact age not stated.

malignant lesions were found. Mahon and Forsee [14] removed 55 round lesions from patients at Fitzsimons Army Hospital, where young and middle-age groups predominate, and found a 7% incidence of malignancy; our experience with a similar group of military-age patients is in close agreement.

Seven series of cases, including 369 patients, have been published in which the age range extended to persons under 35 (Table 2). Only one primary bronchogenic carcinoma is reported for the age group 34 or under, and so its calculated incidence in persons under 35 would be 0.27%. In view of this, the reported mortality rate (1.3 to 3.8% ‡) for surgical excision of unidentified round lesions appears significantly greater than the incidence of primary bronchogenic carcinoma for this age group.

CALCIFICATION FACTOR

The roentgenologic demonstration of calcium within a pulmonary lesion virtually excludes malignancy in the opinion of many authors.§ Occasionally a metastatic osteogenic sarcoma, adenoma of bronchus, malignant change in a teratoma or chon-

‡ References 1, 2, 4, and 16.
§ References 2, 4, 7, 9, and 12.

droma, or the rare instance in which a carcinoma develops around a stone in the lung is reported; however, these conditions are so rare as to hardly merit consideration. Culver [19] states that to his knowledge calcium has never been demonstrated by x-ray examination in primary malignant disease of the lung. It is very important, therefore, to do complete roentgenographic studies including laminography in an attempt to demonstrate calcification within a given lesion.

The majority of nodules which calcify are tuberculomas. Definite rules regarding management of these lesions have not been formulated. Some authors feel that all should be removed, because of their tendency to break down and activate an old tuberculosis.‖ Mitchell [22] concluded in his study of 40 patients at the Trudeau Sanatorium that one in four of such infiltrates will lead to progression of tuberculosis if it has been treated without benefit of chemotherapy, resection, or permanent collapse. He did not state whether any of the lesions in his study were calcified, however. Mahon and Forsee [14] demonstrated the presence of tubercle bacilli in a large percentage of noncalcified tuberculomas which had been excised and found no organisms in lesions which were calcified. Culver, Concannon, and MacManus [19] state that a calcified tuberculoma is of no great risk to the patient and can be left in situ.

Other solitary lesions of the lung which calcify include old pyogenic abscess, nonspecific granuloma, granuloma due to coccidioidomycosis or histoplasmosis, foreign bodies, parasites, pleural plaques, and hamartomas. Probably in none of these is surgery necessary or indicated.

INADEQUACY OF CLINICAL DIAGNOSTIC METHODS

Reasons for the difficulty in the diagnosis of isolated round pulmonary lesions have been discussed in many publications.¶ In coin lesions history and physical examination have rarely been of differential diagnostic value. Bacteriological examination is similarly not helpful as a diagnostic aid.

Cytology.—Cytologic examination of sputum or bronchial washings does not often aid the physician in the diagnosis of isolated round pulmonary lesions, owing, primarily, to the high incidence of false-negative findings. In carcinoma of the lung of all types false-negative tests are encountered in 18 to 40% of the cases.# Since many peripherally located lesions do not communicate with the bronchus, it is reasonable to assume that negative cytology would be a general rule. Woolner and McDonald,[18] for example, could not detect tumor cells in the sputum of a single one of the eight patients with carcinoma. This should not be taken to mean that cytologic examination of the sputum is a useless procedure in evaluating the peripherally situated tumor. On the contrary, if the test is positive, it has great diagnostic significance. Unpublished data from this hospital indicate a 92% chance of malignant disease being present if tumor cells are seen in the sputum or bronchial washings.*

Bronchoscopy.—Bronchoscopy adds little useful information in evaluating these peripheral lesions, since these are generally beyond the range of bronchoscopic visi-

‖ References 1, 8, and 11.

¶ References 1, 4, 5, 7, 11, 12, and 21.

References 1, 18, and 20.

* Ernst, K. F.: Personal Communication to the authors.

bility. It has been abandoned by many, who claim that it contributes little to a specific diagnosis in a patient who will come to surgery irrespective of the bronchoscopic findings.†

Skin Tests.—Positive skin tests for tuberculosis, coccidioidomycosis, and histoplasmosis only indicate that the disease has been or is present but are of little help in identifying the etiology of coin lesions. Skin testing for tuberculosis, coccidioidomycosis, histoplasmosis, etc. in selected cases may help one speculate as to which disease is present. For example, the index of suspicion of malignant disease would be increased in the case of the rare elderly person who has a "coin" lesion and a negative tuberculin skin test. Forsee, Tempel, and Scott [23] recently reported the tuberculin skin test to be positive in 99.5% of patients proved bacteriologically to have pulmonary tuberculosis on whom surgery has been performed for localized lesions (tuberculoma) in the lung. Likewise, the appearance of a positive skin reaction to coccidioidomycosis in a young soldier recently stationed in an area endemic for coccidioidomycosis would be significant if he were being evacuated for a pulmonary infiltration. Skin tests have one great fault, however, since they will not distinguish between carcinoma and inflammatory lesions. Therefore, their usefulness in the population at large is quite limited.

Roentgenographic Studies.—Roentgenographic studies are of value in detecting pulmonary infiltrates but not in specifically identifying them. Size or shape of the lesion cannot be used to rule out carcinoma. If the isolated lesion has a well-defined border, a benign condition is suggested but is certainly not proved. The fact that a shadow remains constant in size over an extended period of time should not lead one into a feeling of false security. Although it is reasonable to assume that most lesions which have not changed in appearance for four years or more are benign, there are exceptions. Rigler [17] observed several such cases over a period of two to three years and one case seven years, only to have the true nature of the tumor manifest itself as regional or distant metastasis. Husfeldt and Carlsen [6] reported a 57-year-old woman who had been observed for 27 months and three other patients observed from 3 to 14 months in whom the pulmonary shadow remained constant in size only to have the diagnosis of carcinoma eventually become self-evident. On the other hand, a nodule which does progressively enlarge is not necessarily malignant. Bronchial cysts, hamartomas, tuberculomas, and other granulomas often increase in size over a period of months or years.

Malignant Metastasis to Lungs.—Since 26% of all malignant growths metastasize to the lung, in some of which instances a solitary nodule may appear, it is important to search for a primary lesion. History of a previous or a simultaneous malignant condition is strongly suggestive that the lung lesion is a metastasis. However, it is obvious that two separate lesions can coexist, as reported by Hood and co-workers,[2] who found unrelated lesions in 2 of 19 patients giving a history of previous malignant disease. In the literature, 4.2% of coin lesions reported are malignant metastases (Table 1).

Lung and Scalenus Node Biopsies.—Lung biopsies have been reported on patients with coin lesions, but one has difficulty in obtaining a biopsy specimen, due mainly to lack of accuracy in locating a small coin lesion with x-ray and fluoroscopy. Insertion of a biopsy needle more than 2 or 3 cm. into the lung frequently produces

† References 1, 3, 7, and 11.

bleeding, pneumothorax, and air embolism.[24] Scalenus node biopsy is another diagnostic aid, but its main use lies in diagnosis of hilar and mediastinal enlargement and infiltrative lung lesions.[25] In a series of 187 cases reported by Shefts and co-workers, only 67 positive biopsies were obtained, of which 38 were sarcoid and 13 were bronchogenic carcinoma.[26]

STUDY OF MATERIAL

The cases reported in the present series fall in the relatively young age group indigenous to a military hospital, the average age of the patients being 32 years (Table 3). Five had symptoms referable to the chest. In the remainder the lesion was found on routine roentgenographic examination. There were no specific preoperative diagnoses made in any of the patients, despite complete clinical studies. Calcification within the lesion was evident on the roentgenograms in Cases 2, 3, 5, and 9. It is felt, in retrospect, that these four patients could have been spared the operative procedure, since none of the lesions encountered would be considered dangerous.

In Case 2, that of a 63-year-old white man, the sputum cytologic examination was positive for malignant cells; therefore our suspicion of bronchogenic carcinoma

TABLE 3.—*Data on Fourteen Additional Isolated Circumscribed Pulmonary Lesions*

	Diagnosis	Age, Yr.		Diagnosis	Age, Yr.
1.	Primary bronchogenic carcinoma	42	8.	Nonspecific granuloma	47
2.	Tuberculoma	63	9.	Nonspecific granuloma	30
3.	Tuberculoma	33	10.	Coccidioidal granulmoa	26
4.	Tuberculoma	22	11.	Coccidioidal granuloma	22
5.	Tuberculoma	21	12.	Chondroma	30
6.	Tuberculoma	20	13.	Hamartoma	22
7.	Nonspecific granuloma	53	14.	Bronchial cyst	22

was very high. The lesion turned out to be a calcified tuberculoma, further evidence that calcium within a lesion indicates a benign condition, despite other clinical findings.

Case 1 was that of a 42-year-old white man who was retired from the Army in 1948 because of valvular heart disease. During 1951-1952 he had been observed in the outpatient clinic at intervals of six months or less. In the interval between visits a round shadow appeared over the left upper lung field. Cytologic studies of sputum and pleural fluid were negative for malignant cells. Nevertheless, within two months of its detection by x-ray studies, the lesion was removed and proved to be epidermoid carcinoma of the bronchus. Unfortunately, within the year skeletal metastases occurred. This case serves to emphasize the fact that cytologic studies of the sputum in cases of peripheral circumscribed carcinoma of the lung are unreliable for purposes of excluding the diagnosis of a malignant condition and also that close medical observation and serial roentgenograms of the chest are not the answer to detection of bronchogenic carcinoma in its early curable stage, if such a stage ever exists.

Ten cases (72%) had nodules of an inflammatory nature, which is in keeping with the expected high incidence of this type of lesion in young persons. The relatively large number of coccidioidomycosis cases reflects the fact that some of our patients resided in an area endemic for the disease (San Joaquin Valley). The

correct diagnosis was suspected in these cases on the basis of history and the demonstration of positive coccidioidin skin tests; however, the causative organism could not be isolated except from the excised lesions.

COMMENT

Experience has shown that the majority of undiagnosed solitary circumscribed intrapulmonary lesions (1) endanger the health or life of the afflicted person and (2) defy all diagnostic measures short of excision biopsy.

The recent trend in management of such pulmonary infiltrates has been to excise them as soon as possible, on the presumption that they are either early bronchogenic carcinomas or unstable inflammatory lesions.

Since thoracotomy carries a definite morbidity and mortality rate, there is a need for objective data which might spare selected patients such an operation.

Of 714 histologically proved isolated round pulmonary lesions reported in the literature, 35.8% were malignant tumors, 40% were of an inflammatory nature, 12.5% were benign tumors, and the remaining 12.5% were a heterogeneous group of conditions.

In a series of 369 patients reported, in which the age range extended to include persons under 35, the incidence of primary bronchogenic carcinoma was 0.27%, a much lower figure than has been heretofore indicated in the literature.

The incidence of malignant change in single noncalcified pulmonary nodules in persons over the age of 50 was 44 to 70%.

Calcified nodular pulmonary lesions are not malignant tumors, in all probability. If they are calcified and of an inflammatory nature, the danger of their breaking down to reactivate an infection is negligible. Therefore, the lesion which contains calcium is not of significant danger to the patient and can be left in situ in asymptomatic persons.

All undiagnosed noncalcified lesions in old persons should be excised if there are no general contraindications to surgery.

Most undiagnosed noncalcified lesions in young persons should be excised, not because they are likely to be malignant but because the majority are unstable foci of inflammatory disease.

SUMMARY

The recent literature on solitary circumscribed lesions of the lung is reviewed. The significance of the patient's age and the factor of calcification within the lesion is discussed in relation to the need for surgical or nonsurgical management of a given patient. Data on 14 additional histologically proved cases are recorded.

From this study it appears that the person under 35 years of age who has a "coin" lesion in the lung has slight chance of having a bronchogenic carcinoma. If the lesion is calcified it is benign, in all probability, regardless of the patient's age. If it is calcified and of an inflammatory nature it is harmless to the patient if left in situ.

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EFFECT OF CORTISONE ON THERAPEUTIC EFFICACY OF ANTIBIOTICS IN EXPERIMENTAL INFECTIONS

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THE ADMINISTRATION of cortisone to severely ill patients often results in marked, though transient, symptomatic improvement, suppression of fever, and apparent reduction in the "toxic state." Physicians therefore are tempted to employ cortisone as an aid in treatment in the hope of tiding a patient over the severest part of an illness until other therapeutic measures can take effect. It is generally known * that cortisone and corticotropin tend to promote the spread of infections and to activate latent infectious processes. Therefore antimicrobial agents are usually administered together with the hormone in such instances to "cover" the potential deleterious effect of cortisone on an existing infection. It is assumed that the hormone will not interfere with the therapeutic efficacy of the antimicrobial agents. This assumption rests on scanty evidence. Several investigators found that cortisone or corticotropin enhances experimental infections with pneumococci or streptococci in laboratory animals but that large doses of penicillin are nevertheless curative.† In guinea pigs infected with tuberculosis Molomut and Spain [8] found a deleterious effect of cortisone on the response to streptomycin but Weimer and co-workers [9] did not.

In clinical therapy of human infections with salmonellae or rickettsiae, cortisone appeared to be a useful adjunct to antimicrobial drugs.‡ It is not possible to decide whether cortisone favored or impeded the suppression of infecting micro-organisms in these instances. Likewise, the reports of Boling and co-workers [12] and Jahn and his associates [13] do not permit an exact evaluation of the interaction of cortisone and antimicrobial therapy.

In view of this apparent gap in knowledge it was thought desirable to evaluate the quantitative effects of cortisone administration on the results of antibiotic therapy in experimental infections in mice. This paper reports the results of a series of experiments designed to control the many variables as rigidly as possible, in the hope of arriving at conclusions that might permit extrapolations to human therapy and generalizations on the nature of the interactions. The initial experiments have been presented in a preliminary report.[14]

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* References 1 and 2.

† References 3-7.

‡ References 10 and 11.

MATERIALS AND METHODS

Bacterial Infections.—Klebsiella pneumoniae (AD) and Streptococcus pyogenes (C 203) were employed as infecting agents. Suspensions of highly virulent organisms in milk were kept in the frozen state at —40 C. These stock suspensions were inoculated into Difco Proteose Peptone No. 3 broth with 5% rabbit blood and incubated at 37 C. for 20 hours. Such broth cultures were suitably diluted and injected intramuscularly into mice, as described previously.[15] The number of viable organisms in the culture was estimated by serial dilution and plate count. For Klebsiella AD the LD_{50} consisted of 50 to 100 organisms injected intramuscularly in a volume of 0.1 ml. The LD_{50} of Streptococcus C 203 was 10 to 50 organisms administered by the same route.

Experimental Animals.—White swiss mice weighing 15 to 19 gm. were obtained from two commercial sources. Mice from these sources have been used for several years in this laboratory. They were known to be free from manifest spontaneous infection, and their spontaneous death rate was less than 1%. They were uniformly susceptible to the experimental infections employed. Following infection with more than 10 LD_{50} of either bacterium, 98% of the animals succumbed to a uniform disease process. With the Klebsiella deaths occurred between two and five days after injection; with the Streptococcus, between five and seven days. The heart blood cultures of moribund animals regularly yielded the infecting organism in pure culture.

Drugs.—Cortisone acetate in a stable suspension was supplied by Dr. E. Alpert, Merck & Company, Inc. The material was suspended in saline solution, and the daily dose was injected in a volume of 0.2 cc. subcutaneously to mice, beginning either 24 hours before the infection or 6 hours after the infection, and continued for five days. The total amount of cortisone injected per mouse never exceeded 1 mg. and usually was 0.75 mg. in five days (approximately 8 to 10 mg. per kilogram per day). The antibiotics penicillin G potassium, streptomycin sulfate, and chlortetracycline hydrochloride (Aureomycin, Lederle) were crystalline commercial preparations. Solutions of suitable concentration were prepared freshly in saline solution and were injected intraperitoneally or subcutaneously in a volume of 0.2 ml. according to the various dosage schedules detailed in the text.

Experimental Procedure.—Groups of 20 to 50 animals were infected and treated with various dosage levels of antimicrobial agents. Alternate groups received cortisone during the period of antibiotic therapy. The animals were carefully observed for the development of the local lesion in the thigh which always preceded the systemic illness and death. Deaths were recorded daily for 14 days after infection, and mean survival times were estimated. The differences in mortality rates of different groups were subjected to the χ-square test for determination of statistical significance.

RESULTS

1. *Effect of Cortisone on Uninfected Host.*—In order to evaluate critically the influence of cortisone on the response of infected animals to antibiotic treatment it was essential to employ doses of cortisone which would be devoid of harmful side-effects. Others have employed daily doses of cortisone ranging from 0.25 mg. to 5.0 mg. per mouse.§ These amounts of cortisone led frequently to lethargy, weight loss, ruffled fur, and other signs of harmful side-effects and occasionally resulted in the death of animals.[17] The largest dose of cortisone which was uniformly well tolerated by mice of 18 to 19 gm. in this laboratory was 0.2 mg. daily for five days. The majority of experiments was performed with 4-week-old animals of 15 to 16 gm. average weight. These mice tolerated a dose of 0.15 mg. cortisone administered subcutaneously daily for five days without any manifest side-effects. In more than 350 control mice receiving a total dose of 0.75 mg. cortisone there was not a single death. The only overt effect of this amount of cortisone was a transient delay in weight gain, as depicted in Chart 1. In comparison with animals receiving saline solution only, the treated mice failed to gain weight while receiving cortisone, but

§ References 1, 3, 16, and 17.

they then resumed their weight gain at an accelerated rate, so that their weight equaled that of the controls 15 days after cortisone was discontinued. In mice receiving 0.75 mg. cortisone in five days no instance of activation of latent infection was observed during the 15-day observation period. It was concluded that the dose of cortisone employed (approximately 10 mg. per kilogram per day) was of a magnitude comparable to that used clinically and would not distort experimental results by gross disturbances of physiological processes.

2. Effect of Cortisone on Therapeutic Effectiveness of Antibacterial Agents in Lethal Infections.—Groups of mice were given 0.15 mg. cortisone daily subcutaneously for five days. Twenty-two hours after the first injection they were injected intramuscularly with 1,000 LD_{50} of either Streptococcus C 203 or Klebsiella AD. Treatment with antibiotics was instituted six hours later, as detailed in Table 1. Parallel groups of animals were treated in an identical fashion but received no cortisone. The death rates in groups with or without cortisone were compared.

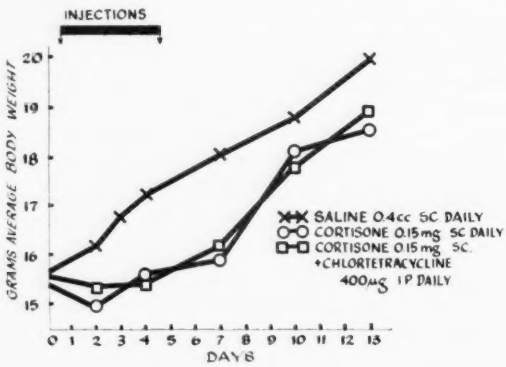

Chart 1.—Effect of cortisone on body weight.

In many, but not all, dosage schedules the death rates in animals pretreated with cortisone were significantly higher than in similar groups not receiving cortisone, as illustrated by results shown in Table 1, A. This apparent interference of cortisone with the therapeutic efficacy of bactericidal (penicillin, streptomycin) as well as bacteriostatic (chlortetracycline) drugs was shown with both infecting organisms (Streptococcus and Klebsiella). It seemed possible, however, that the treatment with cortisone prior to infection had so prepared the mice that the infecting organism could spread more widely and rapidly, thus making antimicrobial treatment less effective. Therefore, treatment with cortisone was begun in other groups of mice after infection, at the inception of antimicrobial therapy. As seen in Table 1, B, significant differences in mortality rates were again encountered between groups with and without cortisone. In these experimental animals the infection was well established before either cortisone or antibiotics were administered, and steroid and antibiotics were injected throughout the same period of time.

Thus the initial experiments indicated that cortisone in well-tolerated amounts depressed the therapeutic effectiveness of antibiotics in lethal infections of mice. Quantitative studies were then undertaken to determine the characteristics and magnitude of this effect.

3. *Influence of Size of Bacterial Inoculum.*—Infectious agents sometimes multiply more freely and reach higher population levels in hosts receiving cortisone than in untreated individuals of the same species.|| Since normal host mechanisms tend

TABLE 1.—*The Influence of Cortisone on Therapeutic Efficacy of Antibiotics in Lethal Infections of Mice*

Infection	Antibiotic, γ/Mouse *	Cortisone, Mg./Mouse *	Dead/Total	% Death	P
A. Cortisone administration started 22 hr. before infection					
Streptococcus 1,000 LD_{50}	P 24 subcutaneously	....	16/24	66	0.02
	P 24 subcutaneously	0.75	24/25	96	
	Au 250 subcutaneously	....	1/24	4	0.002
	Au 250 subcutaneously	0.75	12/25	48	
Klebsiella 1,000 LD_{50}	St 180 intraperitoneally	....	1/30	3	0.01
	St 180 intraperitoneally	1.0	10/30	33	
	Au 2,400 intraperitoneally	....	3/25	12	0.001
	Au 2,400 intraperitoneally	1.0	18/25	72	
.....	.....	1.0	1/76	1.3	....
.....	.....	0.75	0/123	0	
B. Cortisone administration started 6 hr. after infection					
Streptococcus 1,000 LD_{50}	P 240 subcutaneously	....	2/20	10	0.009
	P 240 subcutaneously	0.75	11/20	55	
Klebsiella 100 LD_{50}	St 150 intraperitoneally	....	16/27	59	0.03
	St 150 intraperitoneally	0.75	24/27	89	
Klebsiella 10 LD_{50}	Au 500 intraperitoneally	....	19/38	50	0.01
	Au 500 intraperitoneally	0.75	32/40	80	
.....	.....	0.75	0/68	0	....

* All infecting doses were administered intramuscularly; cortisone, subcutaneously; antibiotics, subcutaneously or intraperitoneally. Total doses of all materials were administered in five equal daily doses. All antibiotic therapy started approximately five to six hours after infection. P, penicillin G potassium; St, streptomycin sulfate; Au, chlortetracycline hydrochloride.

TABLE 2.—*Size of Infectious Inoculum and Depressant Effect of Cortisone in Antibiotic Treatment of a Klebsiella Infection in Mice*

Inoculum of K. Pneumoniae, LD_{50} Injected, No.	Antibiotic, γ/Mouse *	Cortisone, Mg./Mouse *	Dead/Total	% Death	P
7	.....	....	9/10	90	....
70	.....	....	30/30	100	
70	Au 2,000	....	1/20	5	....
70	Au 2,000	0.75	1/24	4	
700	Au 2,000	....	4/31	13	....
700	Au 2,000	0.75	4/25	16	
7,000	Au 2,000	....	6/20	30	0.04
7,000	Au 2,000	0.75	16/25	64	
70	Au 1,000	....	2/24	8	0.001
70	Au 1,000	0.75	16/25	64	
700	Au 1,000	....	6/14	43	0.4
700	Au 1,000	0.75	17/27	63	
500	St 150	....	5/24	21	0.1
500	St 150	0.75	11/25	44	
5,000	St 150	....	15/27	55	0.02
5,000	St 150	0.75	24/27	89	
5,000	St 500	....	3/27	11	0.6
5,000	St 500	0.75	7/27	26	

* Total amounts stated in the table were injected in five equal daily doses. The first dose of both cortisone and drug was administered five to six hours after infection. The infective dose of Klebsiella was injected intramuscularly, the antibiotic intraperitoneally, and the cortisone subcutaneously. Au, chlortetracycline hydrochloride; St, streptomycin sulfate.

to restrict the proliferation of small inocula more than that of large ones, it was of interest to determine the influence of graded sizes of the infectious inoculum upon the observed cortisone effect.

|| References 1 and 2.

Table 2 summarizes a series of pertinent observations, in which constant doses of antimicrobial agents were tested against increasing infectious inocula. Alternate groups of mice received cortisone after the infection. The results suggested that the number of bacteria inoculated influenced the depression of antimicrobial effectiveness of cortisone. However, the size of inoculum and the total antibiotic dose were clearly interrelated in determining the cortisone effect. When the inoculum was large and the resulting infection rapidly overwhelming, cortisone interfered with large doses of antibiotic. When the inoculum was relatively small and the resulting infection more gradual, cortisone did not interfere with large, rapidly curative doses of anti-

TABLE 3.—*Antibiotic Dosage and Depressant Effect of Cortisone in Antibiotic Treatment of Lethal Infections in Mice*

Inoculum, Organism Injected Intramuscularly	Antibiotic, γ/Mouse *	Cortisone, Mg./Mouse *	Dead/Total	% Death	P
Klebsiella 2,000 LD_{50}	Au 600	....	25/25	100	....
	Au 600	0.75	24/24	100	
	Au 1,200	....	12/25	68	0.03
	Au 1,200	0.75	24/25	96	
	Au 2,400	....	3/25	12	0.001
	Au 2,400	0.75	18/25	72	
	Au 4,800	....	0/25	0	0.05
	Au 4,800	0.75	5/25	20	
	Au 10,000	....	0/20	0	0.3
	Au 10,000	0.75	4/30	13	
	.....	....	84/84	100	....
	St 60	....	24/30	80	0.1
	St 60	0.75	29/30	93	
	St 180	....	1/30	3	0.01
	St 180	0.75	10/30	33	
	St 600	....	0/29	0	....
	St 600	0.75	0/28	0	
Streptococcus 1,000 LD_{50}	Au 50	....	14/24	58	0.08
	Au 50	0.75	20/25	80	
	Au 250	....	1/24	4	0.002
	Au 250	0.75	12/25	48	
	Au 500	....	1/23	4	0.1
	Au 500	0.75	7/24	29	
	.....	....	41/41	100	....
	P 3	....	25/25	100	....
	P 3	0.75	24/25	96	
	P 9	....	19/24	79	0.2
	P 9	0.75	23/25	92	
	P 30	....	12/24	50	0.01
	P 30	0.75	21/24	83	
	P 90	....	13/24	54	0.7
	P 90	0.75	15/24	63	

* Total amounts injected in five equal daily doses. Sequence of injections same as in Table 2. Au, chlortetracycline hydrochloride; St, streptomycin sulfate; P, penicillin G potassium.

biotic but did impair the effectiveness of smaller amounts of drug. The depressant effect of cortisone was most evident when the relationship between severity of infection (i. e., size of inoculum) and dose of antimicrobial agent was such as to permit cure of most, but not all, animals in the absence of cortisone (Table 2).

4. *Influence of Dose of Antimicrobial Agent and Nature of Antimicrobial Action.*—The relationship established in the preceding section made it mandatory to determine more precisely the role of antibiotic dosage on the cortisone effect. Accordingly, groups of animals infected with a uniform inoculum of either Streptococcus or Klebsiella were treated with increasing doses of chlortetracycline, streptomycin, or penicillin. Alternate groups received cortisone. Results of representative experiments are given in Table 3 and Chart 2. It is apparent that the cortisone effect was

most significant in the range of moderate antibiotic effectiveness. For obvious technical reasons the effect was absent when the antimicrobial agent alone failed to give a significant cure rate. When an antibiotic was administered greatly in excess of the minimum curative dose the depressant effect of cortisone was likewise no longer significant.

The nature of the antimicrobial agent also played a role in determining the magnitude of the cortisone effect. Cortisone interfered much more with the therapeutic effectiveness of the predominantly bacteriostatic chlortetracycline than with the predominantly bactericidal penicillin or streptomycin (Table 3 and Chart 2). This suggests that cortisone depresses host mechanisms which aid in the control

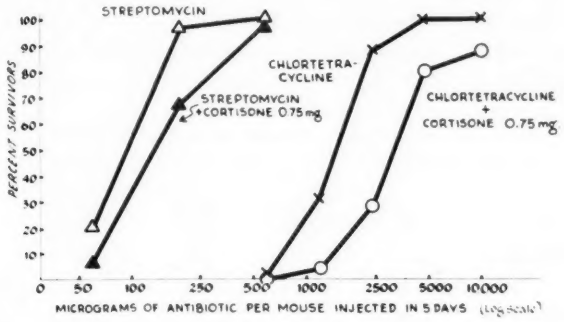

Chart 2.—Effect of cortisone on the therapeutic efficacy of antibiotics in mice infected with Klebsiella.

TABLE 4.—*Bactericidal Synergism of Antibiotics Overcomes Cortisone Effect in Streptococcus Infection of Mice*

Streptococcus, LD_{50}	Antibiotic, γ/Mouse *	Cortisone, Mg./Mouse *	Dead/Total	% Death	*P*
1,000	P 120 + St 800	....	1/22	4.5	....
1,000	P 120	....	7/22	31.8	
1,000	P 120	0.75	15/23	65.2	0.05
1,000	P 120 + St 800	0.75	2/23	8.7	
1,000	St 800	....	24/24	100.0	0.001
.....	.....	0.75	0/29	0.0	

* Total amounts stated in table were injected in five equal daily doses. The first dose of both cortisone and drug was administered five to six hours after infection. The infective dose of Streptococcus (C 203) was injected intramuscularly; the antibiotics, subcutaneously, and the cortisone, subcutaneously into another area. P, penicillin G potassium; St, streptomycin sulfate.

of infection by bacteriostatic antibiotics and thus diminishes the over-all therapeutic effectiveness of such agents. Perhaps bactericidal antibiotics in curative doses do not depend to as great an extent on host mechanisms and thus are less influenced by cortisone. In excessively large doses chlortetracycline behaved like a bactericidal drug.

Experimental support for this hypothesis is presented in Table 4. Penicillin and streptomycin are known to exert a synergistic bactericidal effect against Streptococcus C 203 in vitro.[18] A similar synergistic effect was evident in vivo upon the addition of an inactive amount of streptomycin (800 γ per mouse) to a subcurative dose of penicillin (120 γ per mouse). The subcurative penicillin dose was subject

to the depressant effect of cortisone, but the synergistic combination of the two drugs was not affected. Probably the rapidly bactericidal drug combination was largely independent of host mechanisms for cure of the infection.

5. *Influence of Cortisone on Therapeutic Efficacy of Antimicrobial Agents in Sublethal Infections.*—All experiments presented thus far utilized experimental infections that were uniformly lethal to the host. The majority of human infections are not of comparable severity, and normal host defense mechanisms often lead to recovery. The administration of antimicrobial agents infrequently makes the difference between life and death, but usually only promotes more rapid recovery from the illness. It was of interest to evaluate the possible role of cortisone in the recovery of experimental animals from a sublethal infection in which antibiotics merely improved the spontaneous high rate of recovery.

A sublethal infection was produced in mice by the intramuscular injection of a strain of Streptococcus C 203 which had been repeatedly subcultured on artificial

TABLE 5.—*Influence of Cortisone on the Therapeutic Efficacy of Antibiotics in Sublethal Infection of Mice with Streptococcus C 203 of Low Virulence*

Infection	Penicillin, γ/Mouse *	Cortisone, Mg./Mouse *	Dead/Total	% Death	P
Streptococcus	..	...	8/34	23.5	0.01
Streptococcus	..	1.0	23/29	78.2	
.....	..	1.0	1/49	2.1	....
Streptococcus	12	...	1/50	2.0	0.005
Streptococcus	12	1.0	26/48	54.2	
Streptococcus	48	...	1/50	2.0	0.01
Streptococcus	48	1.0	11/50	22.0	
Streptococcus	300	...	0/50	0.0	0.3
Streptococcus	300	1.0	7/48	14.6	

* Penicillin administered subcutaneously in four equal daily doses, beginning 24 hours after infection. Cortisone administered subcutaneously in five equal daily doses, beginning 24 hours before infection.

media and had lost much of its original virulence. This organism was lethal for only about one-fourth of the injected animals. Cortisone enhanced this infection, so that three-fourths of the animals died (Table 5).

Even minute doses of penicillin cured virtually all animals of the sublethal infection. However, in the presence of cortisone the death rate remained high in spite of penicillin treatment unless the penicillin dose was at least 25 times larger than the dose usually associated with recovery in animals not receiving cortisone. The implications of these findings for the treatment of human sublethal infections are discussed below.

6. *Time Relationship of Cortisone Action and Antibiotic Treatment.*—The results presented in Tables 2 to 5 were obtained by the concurrent administration of cortisone and antibiotic throughout the same period of time after infection. Because of the protracted action of cortisone, it was considered that antibiotic effects might wear off sooner than cortisone effects and thus the "infection-enhancing" property of cortisone might prevail. In this fashion the cortisone effect might outlast antibiotic "coverage," rather than interfere more directly with antimicrobial therapy. To rule out this possibility a series of experiments was conducted

in which cortisone administration was limited to 4 days after infection but antibiotic therapy continued for an additional 24 hours. In this fashion antibacterial action should outlast cortisone effects.

Typical results are given in Table 6, again showing marked cortisone depression of antimicrobial therapy. The time of death was similar in groups with and without cortisone, and the average day of death (ADD) was virtually the same in comparable groups. Thus there was no evidence to support the possibility that the excessive deaths in groups receiving cortisone occurred later than in controls.

7. Observations of Mode of Action of the Cortisone Effect.—Cortisone in concentrations up to 2.0 mg. per milliliter had no effect whatsoever on the growth rate of micro-organisms in vitro or on the level of total viable population reached. Likewise, cortisone failed to influence the bacteriostatic or bactericidal effect of antimicrobial agents in vitro. Thus all direct effects of cortisone on micro-organisms or on antimicrobial drugs may be excluded from consideration.

TABLE 6.—*Time of Death from a Lethal Infection Related to Treatment with Antibiotic Alone or Antibiotic plus Cortisone*

Infection	Antibiotic, γ/Mouse *	Cortisone, Mg./Mouse *	Dead/Total	% Death	Day of Death	
					Range	A D D †
Streptococcus	.....	....	18/19	95	4-9	5.9
500 LD_{50}	.....	0.75	22/22	100	4-10	6.2
	P 100	....	2/19	11	3-12	7.8
	P 100	0.75	11/20	55	5-9	7.0
Klebsiella	.....	....	27/27	100	2-4	3.0
1,200 LD_{50}	.....	0.75	18/18	100	2-4	3.1
	St 150	....	16/27	59	3-13	7.1
	St 150	0.75	24/27	89	3-12	6.2
Klebsiella	.....	....	15/15	100	1-4	2.1
2,000 LD_{50}	.....	0.75	15/15	100	2-4	2.8
	Au 2,400	....	3/23	13	8-12	9.7
	Au 2,400	0.75	18/25	68	4-8	6.3

* All infecting doses were administered intramuscularly; cortisone, subcutaneously; antibiotics, intraperitoneally. Total doses of cortisone were administered in four equal daily doses. Total doses of antibiotics were administered in five equal daily doses. All drug injections were begun five to six hours after infection. Symbols of antibiotics are as in Table 1.

† Average day of death.

The intramuscular infections employed in this study were associated with early and massive infiltration of the muscle with polymorphonuclear leucocytes. It was therefore of interest to determine whether the level of circulating leucocytes, their ability to reach the site of inflammation in the muscle, or their phagocytic function might be impaired by cortisone. Many serial leucocyte and differential counts were performed of the tail blood of animals in experimental and control groups. There were no consistent significant differences attributable to cortisone, as illustrated by the representative experiment in Chart 3. This is in agreement with the findings of others.¶ The ability of phagocytes to ingest bacteria was also found by several investigators to be unimpaired by cortisone.# No additional in vitro studies of phagocytic function were performed in the present study.

Histological sections were prepared from the muscle of mice killed at various intervals after infection.* Histological lesions of the same character were found in

¶ References 2, 3, and 6.

References 3, 18, and 19.

* Dr. W. H. Carnes, Department of Pathology, Stanford University, reviewed the sections.

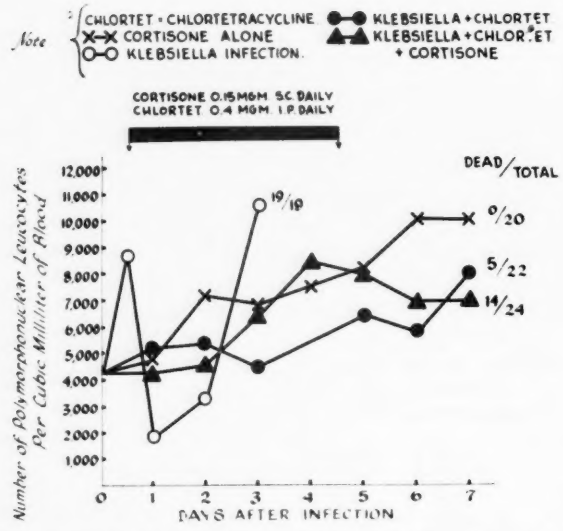

Chart 3.—Effect of cortisone and antibiotic treatment on polymorphonuclear leucocyte count in Klebsiella infection of mice.

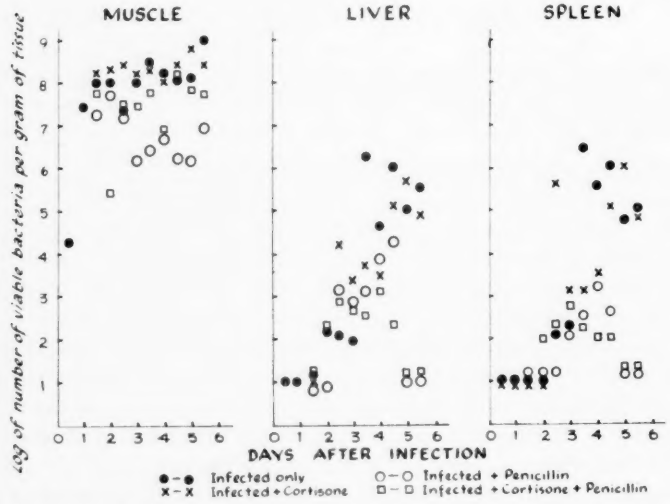

Chart 4.—Distribution of streptococci in mice treated with cortisone and penicillin.

all the groups, and there were no consistent differences between mice treated with cortisone plus antibiotics and controls receiving antibiotics only.

In spite of the failure to demonstrate morphological differences in the tissue response to infection, there might be functional alterations in the mechanisms of localization, removal, or destruction of bacteria. These mechanisms might alter the rate of bacterial proliferation in various organs. Accordingly, the total bacterial populations of muscle, spleen, and liver were determined at various intervals after infection in groups of mice receiving cortisone and antimicrobial agents. The organs were removed with sterile precautions from two or three killed mice, ground with sand, and plated on blood agar in serial dilutions. The total viable count of bacteria per gram of tissue in treated animals was compared with suitable controls. Experiments of this type were performed on mice infected with Klebsiella and treated with chlortetracycline and on mice infected with streptococci and treated with penicillin. In neither case could cortisone be shown to permit a significant increase in the bacterial population as compared with that found in controls. Results of a representative experiment are shown in Chart 4.

COMMENT

The results presented in this paper indicate clearly that cortisone can, under certain circumstances, interfere significantly with the therapeutic efficacy of antimicrobial drugs. The effect is observed within the therapeutic dosage range of cortisone and not merely with excessive doses. It can be demonstrated when cortisone and antibiotic are administered simultaneously for a period of days after infection, and it does not require pretreatment with cortisone. This effect is not due to a direct interaction of drugs, but is mediated through the host. In the intact host animal recovery depends to a considerable extent on natural defense mechanisms when barely curative amounts of antibiotic are employed. Depression of these normal defenses by cortisone results in a striking lowering of the cure rate. This phenomenon is particularly apt to occur with minimal curative or subcurative amounts of the bacteriostatic antimicrobial agents. Such substances suppress microbial multiplication, but eradication of micro-organisms is relegated to the host itself. The depressant effect of cortisone is less marked with curative amounts of primarily bactericidal drugs, like penicillin. Very high concentrations, in excess of curative amounts, of primarily bacteriostatic drugs, like chlortetracycline, behave like bactericidal agents and likewise are but little subject to cortisone depression.

These quantitative relationships make it probable that the depressant effects of cortisone will be manifest in clinical practice only under special circumstances. Clinical antimicrobial therapy generally employs amounts of drug vastly in excess of the curative dose for infections with drug-sensitive micro-organisms. Under such conditions the high drug concentrations probably are rapidly lethal for bacteria and cortisone would have little effect. With drug-resistant micro-organisms, on the other hand, the cortisone depression of antibiotic action may present a real problem. Antibiotic-resistant staphylococci or Gram-negative bacteria are encountered with increasing frequency. In antimicrobial therapy directed against such organisms, maximally tolerated drug doses may only be barely curative, requiring the aid of host mechanisms for recovery of the patient. In such cases cortisone might exert a distinctly harmful effect by disturbing the delicate balance in host-parasite relationship, to the host's disadvantage.

Yet it is precisely in these severely ill, perhaps toxic, patients with overwhelming infections that the temptation might be greatest to employ cortisone for its nonspecific "supportive" effect.† It may be argued that the manifest improvement following cortisone administration will help the patient's defenses to rally to the aid of barely suppressive antimicrobial therapy in drug-fast infections. The experiments presented here lend no support to this view and strongly suggest that the opposite might be the case. The antiendotoxic effect of cortisone must be considered separately.[20]

The nature of the "impairment of host defenses" referred to above remains indefinite. While high doses of cortisone inhibit antibody formation,‡ this effect may probably be discounted in the present experiments. The cortisone dosage employed was low and the infection too rapidly invasive for antibody to play a significant role. A reduction of phagocytic cells either in the circulating blood or at the site of intramuscular infection might explain the phenomenon, but no such reduction could be demonstrated. With the small doses of cortisone employed, the inflammatory response was not demonstrably impaired in histological preparations.[21] Diapedesis of leucocytes and phagocytosis § appeared to be the same in animals receiving antibiotic plus cortisone and controls given antibiotic only. Local necrosis at the site of infection was not significantly increased by cortisone. In agreement with the findings of Martin and Kerby,[24] splanchnic removal of bacteria was not affected by cortisone. This function had been found in earlier studies [25] to be impaired by minimum lethal doses of ionizing radiation, which likewise impaired the therapeutic efficacy of antibiotics.

With only negative findings in the search for the point of action of cortisone in our experiments, it is tempting to implicate an impairment in the ability of phagocytic cells to destroy ingested micro-organisms. This may permit intracellular survival or multiplication followed by reliberation into tissues and blood stream. Experiments are planned to investigate that possibility, suggested also by the work of Clawson and Nerenberg.[26]

From a practical standpoint the nature of the depression of host defense mechanisms by cortisone is of limited importance. Experiments such as presented here, or those reported by Ilavsky and Foley [27] after the present work was completed, suggest caution in the clinical use of cortisone when infection is suspected or established. Cortisone may be specifically contraindicated in those infections caused by antibiotic-resistant micro-organisms in which prompt eradication of the bacteria by antimicrobial agents appears unlikely. If antibiotics are administered to "cover" the infection-enhancing properties of cortisone, the present experiments suggest that very large doses of bactericidal drugs or drug combinations should be recommended.

SUMMARY

In two subacute experimental bacterial infections of mice very small amounts of cortisone markedly interfered with the therapeutic effectiveness of antibiotics. The phenomenon was observed not only when the animals were pretreated with cortisone but also when the administration of both cortisone and antibiotic was

† References 12 and 13.

‡ References 1 and 2.

§ References 22 and 23.

started several hours after infection. The magnitude of this effect depended on the severity of the infection, as determined by the number of bacteria inoculated, and on the dose of antimicrobial drug. It was greatest when the result of antimicrobial therapy without cortisone was subcurative. With a large excess of antibiotic beyond the curative does the reduction of therapeutic efficacy by cortisone was no longer evident.

It is shown that this effect of cortisone is mediated through host defense mechanisms which ordinarily aid subcurative amounts of antimicrobial drug in eradicating the infection in the host. Large amounts of bactericidal drugs which are capable of rapidly killing the bacterial population within the host are not subject to this action of cortisone. Results of experiments on the precise site and mechanism of this cortisone effect remain inconclusive.

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SURVEY OF CLINICAL SIGNIFICANCE OF SERUM MUCOPROTEIN LEVEL

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RECENT reports have stimulated interest in factors responsible for the maintenance of the serum mucoprotein (M) level in health and disease. Winzler and colleagues noted some years ago that a marked increase in the serum M level occurs as a result of inflammatory [1] or neoplastic disease* and after experimental tissue injury.[1] This response in the serum M concentration was presumed to be related to factors of a nonspecific or unknown nature involved in cellular proliferation and tissue breakdown. Several investigators have now demonstrated that divergent changes in the serum mucoprotein (M) level may be observed in patients with certain nosologically or pathologically related diseases. Thus, among the neoplastic diseases, multiple myeloma [3] was associated more frequently with a reduction than with an elevation in the serum M concentration. A rising M level was usually observed in the presence of most forms of progressive obstructive biliary tract disease, whereas infectious hepatitis, homologous serum jaundice, and portal cirrhosis were usually associated with falling or reduced M levels.[4] A reduced M concentration found in "lipoid nephrosis" contrasted with an increased M level observed in acute glomerular nephritis.[5] Recently the suggestion was made that serum mucoprotein may represent an "acute phase reactant" in rheumatic fever,[6] with potential value as a guide to the degree of rheumatic activity. The nonspecificity of this "reactant" is indicated, however, by the marked changes in the serum M level occurring with sterile turpentine abscess [1] or acute myocardial infarction.[7]

That endocrine factors may play a role in regulating the M level was initially suggested by the observation that normal young adult females show significantly lower M level than do normal adult males.[4] In addition, it was noted that reduced M levels occur with unexpected frequency in patients with endocrine deficiency states characterized by pituitary, adrenal, or thyroid dysfunction.[8] These clinical data have now been supplemented by experimental studies in rats, indicating that the serum M level may be partially controlled by the pituitary and adrenal glands.†

It has recently been suggested [8] that the serum mucoprotein (M) level represents the resultant of two sets of factors: (1) hepatic and endocrine functions which

Miss Bernice Gitler gave technical assistance in this study.

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From the Department of Medicine, The Mount Sinai Hospital, and the National Cancer Institute, National Institutes of Health, United States Public Health Service, Bethesda. Md.

* References 1 and 2.

† Reference 9 and Greenspan, E. M.: Unpublished data.

Mucoprotein (M) Concentration in Initial Serum Sample Obtained from 1,533 Adult Patients from a General Medical Service

Diagnosis	Serum M Concentration, Mg./100 Cc.* Increased	Normal †	Decreased	Comment
I. Infections				
A. Acute				
1. Pneumonia, enteritis, phlebitis, cellulitis, prostatitis, bronchitis, influenza, etc.	52	1	0	M increased in >90%; except in patients with acute infectious mononucleosis (and in hepatitis, v. i.)
2. Infectious mononucleosis with tender liver with or without jaundice	7	6	1	
B. Subacute or chronic				
1. Endocarditis, enteritis, colitis, ileitis, sinusitis, pulmonary abscess, diverticulitis, bronchiectasis, etc. (exclusive of biliary tract infections)	69	21	2	M increased in >75% of patients with active subacute or chronic infectious or inflammatory disease
(Ulcerative colitis with marked hepatomegaly ‡	0	2	2)	
2. Tuberculosis (active)	17	2	0	
3. Tuberculosis (probably inactive)	1	10	1	
II. Neoplasms				
A. Benign (excluding cutaneous lesions)				
1. Fibroadenomatous breast disease with fibroid uterus	0	10	5	Low M values suggest possible hepatic-endocrine dysfunction; M normal in most patients with benign neoplasms, excluding gynecological fibroadenomatous lesions; normal M in almost half with cancer of head or neck with or without metastases; increased M in 80% with visceral or lympoid neoplasms; decreased M frequently found in multiple myeloma, and in a few patients with neoplasia plus hepatitis, portal cirrhosis, or estrogen therapy
2. Others, excluding thyroid tumors	1	16	1	
B. Malignant				
1. Carcinoma of head, neck, or cutaneous structures	22	18	4	
(Craniopharyngioma with secondary panhypopituitarism	0	0	2)	
2. Carcinoma of lung, stomach, colon, kidney, prostate, etc. (excluding biliary tract, v.i.)	120	20	5	
(Prostate carcinoma on estrogen therapy	0	1	3)	
3. Leukemia, lymphoma, Hodgkin's disease, etc.	66	15	3	
4. Sarcoma, melanoma	8	5	1	
5. Multiple myeloma	2	2	7	
(All neoplasms with hepatitis or portal cirrhosis	2	9	5)	
(Hepatoma with portal cirrhosis	0	3	2)	
III. Cardiovascular-renal, degenerative, collagen disease, etc.				
1. Congestive heart failure (rheumatic inactive, arteriosclerotic, hypertensive, cor pulmonale, etc.)	23	9	3	M values are normal or high in almost all patients in these categories in Group III
1a. "Cardiac cirrhosis"	0	1	3	
2. Hypertensive or arteriosclerotic cardiovascular-renal disease not in failure; without recent acute thrombotic episodes	8	20	1	
3. Myocardial infarction, acute	8	3	0	
4. Pulmonary infarction, acute	8	0	0	High incidence of increased M values in rheumatic fever and rheumatoid arthritis is contrasted with frequency of normal M values in lupus; the few low M values occured in patients with nephrosis or parenchymatous liver disease
5. Diffuse vascular disease (periarteritis nodosa, dermatomyositis; thrombophlebitis, multiple or recurrent)	10	4	0	
6. Glomerulonephritis, acute or chronic active	8	0	0	
7. Nephrosclerosis or vasculitis with uremia	8	0	0	
8. Nephrotic syndrome, primary type	0	0	6	
9. Nephrotic syndrome, secondary type with carcinoma, or renal vein thrombosis (excluding Kimmelstiel-Wilson syndrome)	0	5	0	
10. Pyelonephritis, chronic; renal calculus; cystopyelitis, etc.	2	7	0	

11. Rheumatic fever, acute, active	15	2	0	
12. Rheumatic heart disease; activity? not in failure	1	5	1	
13. Rheumatoid arthritis, acute, subacute, chronic	16	2	0	
14. Disseminated lupus erythematosus	9	10	1	
15. Arthritis, acute infectious, Reiter's syndrome	4	0	0	
IV. Metabolic disease				
1. Diabetes mellitus (under control with or without acute cardiovascular-renal complications)	10	62	21	Reduced M values in about one-fifth of diabetics and in about one-third of patients with various thyroid disorders; less than half of these patients with low M have overt evidence of hepatitis or cirrhosis
(Diabetes with acute CVR complication	4	2	0)	
2. Diabetes mellitus admitted in ketoacidosis	1	2	4	
3. Kimmelstiel-Wilson syndrome	1	3	2	
4. Hyperthyroidism	4	13	11	
(Hyperthyroidism with hepatitis or cirrhosis	0	2	6)	
5. Posthyperthyroidism in the euthyroid state	0	12	3	Low M in 13 of 18 patients with panhypopituitarism or Addison's disease
6. Nontoxic goiter, adenoma, or Riedel's struma	0	7	1	
7. Myxedema, secondary type	0	2	4	
8. Panhypopituitarism	0	2	5	
9. Addison's disease (under treatment)	0	3	8	
10. Hemochromatosis	0	2	0	
11. Pernicious anemia	1	7	1	
12. Macrocytic anemia (unknown etiology)	0	2	0	
13. Iron deficiency enemia	0	2	0	
14. Idiopathic hypercholesterolemia (familial type)	0	2	0	
15. Gout	2	4	0	
16. Senile osteoporosis	0	1	0	
17. Primary hyperparathyroidism	0	1	0	
18. Sprue syndrome idiopathic	1	4	1	
19. Cushings syndrome or induced hyperadrenalism	1	0	0	
V. Disease characterized by hepatomegaly and/or jaundice				
A. Primary parenchymatous hepatic disease				
1. Infectious hepatitis (all cases)	1	12	50	Potential value of M determination in differentiating hepatogenous from obstructive jaundice is seen in the different distribution of these initial M values in Group A as compared to Group B; serial determinations and a comparison with other diagnostic tests are discussed in Reference 8
(Infectious hepatitis with obvious extrahepatic disease	1	6	3)	
2. Homologous serum hepatitis	0	3	17	
3. Portal cirrhosis (all cases)	8	15	71	
(Portal cirrhosis with septicemia, pneumonia, hepatoma, tuberculosis, etc	8	11	3)	
4. Fatty liver degeneration (biopsy) with chronic alcoholism and hepatomegaly	4	4	0	
5. Probable "cardiac" cirrhosis, v.s	0	1	3)	
6. Hepatosplenomegaly with schistosomiasis and multiple intestinal parasitism	0	11	11	
B. Obstructive biliary tract disease				
1. Inflammatory				
a. Acute and chronic cholecystitis	8	1	0	
b. Chronic cholecystitis	6	24	1	
c. Common duct stone	4	5	0	

Mucoprotein (M) Concentration in Initial Serum Sample Obtained from 1,533 Adult Patients from a General Medical Service—Continued

Diagnosis	Serum M Concentration, Mg./100 Cc.* Increased	Normal †	Decreased	Comment
d. Acute pancreatitis	4	0	0	
e. Chronic pancreatitis	5	13	1	
f. Biliary cirrhosis	2	4	0	
g. Cholangitis	9	3	0	
h. Postcholecystectomy syndrome	1	17	1	
2. Neoplastic				
a. Gall bladder or biliary duct	4	5	1	
b. Head of pancreas	9	14	0	
c. Metastases at porta hepatitis from gastrointestinal primary lesions	3	1	0	
VI. Hepatomegaly (tabulated from cases under Groups II and III)				
A. From hepatic metastases				
1. Carcinoma (excluding biliary pancreatic neoplasms shown above)	61	2	0	About 90% of patients with these common forms of hepatomegaly showed high M values
2. Lymphoma or leukemia	41	4	1	
B. From congestive heart failures	22	5	3	
VII. Miscellaneous				
1. Peptic (duodenal or gastric) ulcer	7	39	8	In a small proportion, peptic ulcer was associated with low or high M values
1a. Perforating or penetrating peptic ulcer	5	1	0	
2. Functional gastrointestinal disease	1	19	0	About 90% of neuropsychiatric patients had normal M values
3. Psychoneurosis or psychosis	3	29	1	
4. Acute alcoholism; carbon tetrachloride poisoning	3	1	3	Values were low or high in these acute toxic states
5. Sarcoidosis	2	7	3	
6. Congenital or acquired hemolytic anemia	4	2	0	
7. Polycythemia vera	4	2	0	
8. Hemophilia	1	4	0	
9. Thrombocytopenic purpura	2	1	0	
10. Gynecomastia	0	3	1	
11. Idiopathic menometrorrhagia	0	1	3	
12. Intestinal amebiasis	1	5	0	Low M absent in these patients with Amebic disease
13. Amebic hepatitis or abscess	1	1	0	
14. Intestinal parasitism	1	5	0	
15. Pulmonary fibrosis and emphysema	0	4	0	
16. "Common cold"	0	7	0	
17. Others, including malaria, hypertrophic gastritis; syphilis; myelofibrosis; obesity; parox. noct. hemoglobinuria; Paget's disease; mercury poisoning; sickle-cell anemia; bronchial asthma; osteoarthritis; Reiter's syndrome; status postsurgical resection, etc.	18	43	3	
18. Disease (?), undiagnosed	32	47	8	In these miscellaneous or undiagnosed diseases low M values occurred in from 4 to 8% and high M values in from 25 to 40%

* Measured as biuret peptide.

† Normal values: men, 48 to 75 mg. per 100 cc; women, 40 to 70 mg. per 100 cc.

‡ Cases in parentheses represent a portion of the category immediately preceding.

when impaired lower the M level and (2) unknown factors associated with cellular proliferative or degenerative processes which, when accelerated as in inflammatory, neoplastic, or traumatic tissue changes, tend to increase the M level.

During various studies § on the biological and clinical significance of the serum mucoprotein, data were obtained from more than 1,000 patients with a wide variety of diseases. This paper presents a brief survey of the initial M determination in these patients, not taking into account the subsequent changes which occurred as a result of treatment or of the natural course of disease.

The patients studied during the preliminary phases ‖ of this investigation were hospitalized at the Clinical Research Unit of the National Cancer Institute and the Medical Service of the United States Public Health Service Hospital and the Sinai Hospital, Baltimore, Md. This study was subsequently extended at the medical and surgical services and the outpatient clinics of The Mount Sinai Hospital, New York. Until the first 1,000 cases were obtained, an attempt was made to obtain a representative cross section of case material observed on the medical services. Later, serum specimens were obtained more selectively, from as many patients as possible admitted with hepatomegaly, jaundice, metabolic or endocrine disease, coagulation defects, and various unresolved diagnostic problems. Normal sera were obtained from members of the hospital staffs in apparent good health.

The diagnosis of neoplastic disease was established by tissue biopsy or autopsy examination in all instances. In more than half the patients classified in the Table under biliary tract or liver disease, the clinical diagnosis was confirmed by liver aspiration, laparotomy, or autopsy examination. In many patients, it was difficult to make a single diagnostic classification when two or more unrelated diseases were present in the same patients simultaneously. Certain patients were classified twice under different headings in the exceptional categories indicated in parentheses in the synoptic table.

The methods employed for estimating serum mucoprotein have been fully described in previous papers.¶

RESULTS

The results of the initial serum mucoprotein (M) determinations in 1,533 patients are summarized in the Table, according to the major diagnosis for each patient. These M determinations were classified with a lower normal range [4] for females (40 to 70 mg. per 100 cc.) than for males (48 to 75 mg. per 100 cc.). The Figure graphically illustrates the distribution of high, normal, and low values among 1,290 patients comprising the five major groups of disease in this study.

1. Infectious Diseases.—An increased serum concentration of mucoprotein was observed in 52 of 53 patients with such acute infectious diseases as pneumonia, enteritis, cellulitis, etc. (excluding infectious hepatitis) (Table, Group 1). This group of patients necessarily constitutes a selected series, since only relatively severe cases, requiring hospitalization, were available. No recognizable virus disease other than several cases of influenza was included in this group. A separate classification was made for infectious mononucleosis, because of the frequency of liver involvement. Among the 14 cases of infectious mononucleosis there was a reduced M level in only 1, with normal values in 6 and elevated values in 7. All these patients with infectious mononucleosis presented with some gastrointestinal symptoms and either hepatomegaly or jaundice. The only patient among these 14 who showed a reduction in

§ References 3, 4, 8, and 10 and Greenspan, E. M.: Unpublished data.

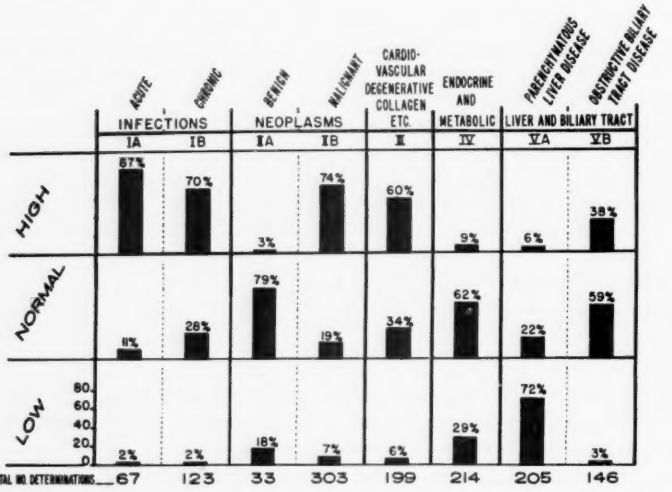
‖ References 3 and 4.

¶ References 4, 7, and 8.

the serum M level was suffering from severe jaundice with features clinically indistinguishable from infectious hepatitis. The correct diagnosis was made only after a very high positive heterophile titer was unexpectedly obtained.

In the series of 123 patients with subacute or chronic inflammatory disease other than of the liver and biliary tract, about 75% showed high M values. The M level was below normal in only three instances in the large group of patients in this category. Two of these three patients had ulcerative colitis, with evidence of severe parenchymatous disease of the liver.

II. Neoplastic Disease.—The M concentration was increased in only 1 of a group of 33 patients with benign neoplasms. There appeared to be an unexpected number of low M values among a small series of women with both fibroadenomatous breast disease and fibroid uterus. No attempt was made in this survey to relate



The distribution of high, normal, or low mucoprotein levels in the initial serum sample from 1,290 patients comprising the five major groups in this study. Additional details concerning the diagnosis in each group are provided in the Table.

these observations to any abnormal hepatic or endocrine function which may have been present among these patients.

Primary cancer originating in the head or neck, with or without regional metastases, was associated with elevated M levels in only about 50% of a total of 44 patients studied. Of the four patients with reduced M levels in this group, two suffered from hypopituitarism secondary to a locally invasive craniopharyngioma.

An approximately 80% incidence of increased M concentrations was observed among 229 patients with leukemia, lymphoma, or carcinoma of visceral origin. Multiple myeloma was the only neoplasm which appeared to be a conspicuous exception to these general observations among patients with neoplasms, since low M levels were found in 7 and normal values in 2 of a total of 11 cases. Apart from the cases of multiple myeloma, there were low M levels in only 8 cases in this group of 229. Three of these eight patients with low M values were receiving estrogen

therapy for diffusely metastatic prostate carcinoma and were in clinical remission; three others were suffering from concurrent hepatitis or cirrhosis plus neoplasm, and the remaining two showed clinical evidence of severe parenchymatous hepatic damage from urethan after developing partial remission in chronic leukemia. Of a total of 16 patients with both neoplastic disease and obvious coexisting hepatitis or cirrhosis, the M level when first measured was low in 5, normal in 9, and increased in only 2. The serial changes in the M level as disease progressed in these and other patients with such "multiple lesions" have been presented in studies published elsewhere.[8]

III. Cardiovascular-Renal, Degenerative, Collagen, and Related Diseases.—An increased serum M concentration was observed in about two-thirds of patients in these general categories. The mucoprotein levels were usually increased during acute cardiovascular complications or intercurrent episodes of cellular necrosis, as in myocardial infarction, pulmonary infarction, or diffuse vascular disease (excluding disseminated lupus erythematosus). The increase in the M level observed in 23 of 35 patients with congestive heart failure may have been related to associated secondary pathologic changes in lungs and other tissues.

Whereas all 6 patients with the nephrotic syndrome (nephrotic stage of glomerulonephritis) showed reduced M levels, 16 patients with glomerulonephritis or nephrosclerosis with uremia showed elevated M levels. When the nephrotic syndrome was secondary to amyloidosis (associated with neoplastic disease or renal vein thrombosis), no low M levels were observed, in the small series of five patients available for study. These cases all showed normal M values in the first serum sample obtained. In several patients with the nephrotic stage of glomerulonephritis the M values slowly increased, until high M values were reached when a frank nephritic stage was evident.

A difference in serum mucoprotein levels in rheumatoid arthritis as compared with those in disseminated lupus erythematosus was also observed. In a group of 18 patients with rheumatoid arthritis 16 showed increased mucoprotein levels, whereas in a comparable group of 20 patients with lupus (all with arthritic manifestations) there were 10 with normal mucoprotein levels. Of 17 patients with active rheumatic fever 15 showed increased M values. A comparison of the M level with other laboratory procedures for assessing rheumatic activity will be published elsewhere.#

IV. Metabolic and Endocrine Disease.—The preponderance of increased M levels in patients with inflammatory, neoplastic, and degenerative diseases was in distinct contrast to the paucity of increased M values and the relative frequency of reduced M levels in patients with metabolic or endocrine diseases. Thus, there were only 19 high M values, in contrast to 61 low M values, in 214 patients with metabolic or endocrine disease. The frequency of low M values was particularly apparent in patients with pituitary, thyroid, or adrenal dysfunction. Only a few of these patients, as indicated in parentheses in the Table, showed obvious clinical or laboratory evidence of liver disease. Nevertheless, among 7 patients with panhypopituitarism there were 5 with reduced M values, and among 11 with Addison's disease there were 8 with low values. The incidence of low M levels in patients with

Elster, S.; Wood, H., and Greenspan, E. M.: To be published.

Addison's disease or hypopituitarism is noteworthy, since there was no associated overt clinical or laboratory evidence of intrinsic liver disease. The observation that the serum M levels were usually normal in a small series of untreated and treated cases of pernicious anemia is of interest in view of the fact that a deficiency of mucoprotein in the upper gastrointestinal tract has been suggested to be of pathogenic significance in this disease.[11]

V. Disease Characterized by Hepatomegaly or Jaundice.—This category comprised pathological conditions in which hepatomegaly or jaundice was a principal clinical feature requiring diagnosis. Group A included 177 cases of infectious hepatitis, homologous serum hepatitis, and portal cirrhosis, whether or not any extrahepatic disease coexisted when the initial serum was obtained. In parentheses below each diagnostic category are included the number of cases in which such obvious extrahepatic disease processes occurred. From the data it may be noted that more than 80% of 83 patients with infectious or homologous serum hepatitis and more than 70% of 94 cases of portal cirrhosis showed low mucoprotein levels, whereas less than 3% of the 146 patients in Group B, with any of the various forms of obstructive biliary tract disease (inflammatory or neoplastic), showed low M levels. Most of the hepatitis-portal cirrhosis group with normal or high M values were suffering from coexistent septicemia, pneumonia, peritonitis, tuberculosis, hepatoma, or ulcerative colitis at the time the initial M determination was obtained.

The M levels in obstructive biliary disease (Group B) were either normal or increased, without correlation with the pathologic nature of the obstructive process. At the time of admission to the hospital such acute inflammatory lesions as cholangitis or cholecystitis appeared to raise the mucoprotein level more consistently than did the presence of a localized tumor of the head of the pancreas. Apparently the presence of localized neoplasm or of a stone was insufficient per se regularly to elevate the M level in the early phases of obstructive jaundice. When obstructive disease continued, the M level often increased, so that in the most advanced stages of progressive obstructive biliary tract disease, as in frank biliary cirrhosis, the M level was found to remain normal or to become elevated rather than to fall to the reduced levels usually found in portal cirrhosis. The fatty infiltration stage of alcoholic cirrhosis was not associated with reduced M levels in eight cases, all proved by biopsy. Approximately half of a group of Puerto Rican patients with hepatosplenomegaly, schistosomiasis, and intestinal parasitism showed low mucoprotein levels. It was impossible to determine whether this was a manifestation of schistosomal disease per se or of previous nutritional factors, which may be related to a relatively high incidence of portal cirrhosis found among such patients.

VI. Hepatomegaly.—The rarity with which patients with the two commonest forms of hepatomegaly, i. e., those due to neoplastic infiltration or congestive heart failure, manifested reduced mucoprotein levels is demonstrated by the tabulation in Group VI. Among 108 patients with hepatomegaly histologically proved to be due to carcinoma, lymphoma, or leukemia, 1 showed a low M value and 6 showed normal levels. Even when the liver was very extensively replaced by metastases, the M level remained elevated. Over 90% of patients with a palpable liver due to metastases showed an increased mucoprotein level (usually above 90 mg. per 100 cc.) when first examined. Because of the frequency of hepatomegaly due to congestive failure, 30 patients with congestive failure of varied etiology (exclusive of hyper-

thyroid heart disease) were studied. Twenty-two of these patients showed increased M levels, 5 were in the normal range, and 3 showed reduced levels. As already noted, clinical diagnosis of "cardiac cirrhosis" was made without histologic proof of the nature of the pathologic process in the liver in these three patients with low M values.

VII. Miscellaneous.—Pathologic conditions not readily classified under the previous categories are tabulated in Group VII. Among 54 patients in whom peptic ulcer was the only diagnosis which was established, there were normal M levels in approximately 75%. It was interesting to note that about 10% showed reduced M values, a finding possibly related to the not uncommon association of peptic ulcer with unrecognized metabolic or endocrine disease. Among 53 patients with a diagnosis of either functional gastrointestinal disease, psychosis, or psychoneurosis, there were 48 normal M values. In a group of 87 patients for whom no definite diagnosis could be established despite symptoms warranting hospital admission, the M values were increased in about 30%, decreased in 10%, and normal in about 60%.

Summary of Results.—The effect of various disorders on the serum mucoprotein (M) concentration may be summarized as follows:

A. Disease associated with increased M levels
   Acute, subacute, or chronic infectious disease
   Malignant neoplastic disease
   Degenerative, thrombotic, or inflammatory vascular processes
   Necrosis or cellular degeneration induced by toxic chemical agents, shock, trauma, or other physical agents (without overwhelming liver damage)

B. Diseases associated with reduced serum M levels
   (1) With hepatic dysfunction
      Infectious hepatitis*
      Homologous serum hepatitis *
      Portal cirrhosis *
      Schistosomiasis and associated disease *
   (2) With endocrine dysfunction
      Panhypopituitarism *
      Addison's disease *
      Thyroid dysfunction (hypothyroidism, hyperthyroidism, or induced euthyroidism)
      Diabetes mellitus
      Fibrocystic breast disease, fibroid uterus
      Prostatic carcinoma receiving estrogen therapy
   (3) Without overt hepatic or endocrine dysfunction
      Nephrotic syndrome (glomerulonephritis) *
      Multiple myeloma *
      Sarcoidosis

C. Diseases in which the absence of reduced serum M level may be of some differential clinical value
   Obstructive biliary tract disease (biliary cirrhosis, cholecystitis, cholangitis, common duct stone, carcinoma of biliary ducts or pancreas)
   Hepatomegaly due to metastases
   Secondary nephrotic syndrome due to amyloid, disseminated lupus, etc.
   Infectious mononucleosis

* Low M values in 50 to 90% of patients.

COMMENT

A multiplicity of serum protein precipitation-flocculation tests has been developed and introduced into clinical medicine during the past three decades. For the most part these tests have provided a more or less crude measure or guide to the status of serum gamma globulin, beta globulin (lipoprotein), albumin, or the albumin-globulin ratio. Relatively little attention has been directed to the carbohydrate-rich alpha globulin fractions, which, in electrophoretic studies, are known to increase characteristically in the presence of extensive inflammatory [12] or neoplastic disease.† The mucoprotein determination represents a convenient indirect method of detecting alterations in a portion of the globulin spectrum, i. e., the alpha globulins, which has heretofore been difficult to study by simple laboratory methods. The serum mucoprotein level appears to be inherently independent [8] of the sedimentation rate, the cephalin-flocculation test, the albumin-globulin ratio, the thymol-turbidity test, the zinc sulfate flocculation, and other serum components commonly measured in clinical laboratories.

The labile, sensitive, and nonspecific character of the M level must be kept in mind in evaluating any single M determination. Serial fluctuations in the M level usually can be correlated with rapid clinical changes in the individual patients. Despite the inherent lability of the M level, the M determination has been a useful laboratory adjunct in a variety of diagnostic problems. In the jaundiced patient the M level was found to be at least as valuable as other available tests [8] commonly employed for differentiating hepatogenous from obstructive jaundice. When dealing with hepatomegaly of unknown origin, the M determination was helpful in distinguishing patients with portal cirrhosis from those with neoplastic hepatomegaly and often called attention to the need for further diagnostic or therapeutic procedures, such as biopsy, laparotomy, supportive medical therapy, etc. Although sufficient data are not yet at hand to determine the relative merits of the M level in evaluating posthepatitis syndromes, there are preliminary data ‡ indicating that the course of chronic parenchymatous liver disease and its superimposed complications may be evaluated with the aid of mucoprotein determinations.

Although the serum mucoprotein determination may be useful in evaluating the activity or extent of inflammatory diseases, particularly rheumatic fever, as reported by Kelly and co-workers,[6] caution in this regard is necessary. The possibility of a change in the M level in either direction, due to superimposed or complicating hepatic or endocrine dysfunction in rheumatic patients, must be considered in interpreting any data. In patients with certain types of organic disease, such as disseminated lupus erythematosus, the frequency of pathologic changes in hepatic or endocrine function as well as in tissue proliferative or degenerative processes may account for the occurrence of both downward and upward variations in M level.

This potential for a bidirectional response in the M level offers the clinician a differential guide not only in diagnosis but in stimulating further work-up of perplexing diagnostic problems. As a screening procedure for organic disease in undiagnosed cases, the M determination would appear to be a useful laboratory adjunct.

The physiological significance of the serum mucoproteins remains an obscure and intriguing problem in view of the wide and rapid fluctuations in serum concen-

† References 15 and 16.

‡ Greenspan, E. M.: Unpublished data.

tration (15 to 300 mg. per 100 cc.) which may be observed in patients with certain diseases.[8] A possible relationship of such changes in the mucoprotein level to alteration in pituitary-adrenal function or to acute stress states has been suggested by some clinical § and experimental [9] evidence that the serum mucoprotein fraction is an extremely sensitive indicator of alteration in tissue and hormonal reactions.

SUMMARY

The serum concentration of mucoprotein (M), an alpha-1-globulin component, normally varies from 40 to 70 mg. per 100 cc. in adult females and from 48 to 75 per 100 cc. in adult males. The present study is a general survey of M determinations in 1,533 patients on a general medical service to ascertain the effects of a diversity of diseases on these levels.

Diseases characterized by inflammatory, neoplastic, degenerative, thrombotic, or traumatic tissue changes were associated with a significant incidence of increased serum M levels. Reduction in serum M levels was found in from 70 to 90% of patients with infectious hepatitis, homologous serum hepatitis, portal cirrhosis, panhypopituitarism, and Addison's disease. More than half of the series of patients with nephrosis and myeloma showed low serum M concentrations. Approximately one-fourth of patients with thyroid disorders and one-sixth of patients with diabetes mellitus had low mucoprotein levels.

Approximately half of all patients with low M values in this study presented with portal cirrhosis, infectious hepatitis, or homologous serum hepatitis; one-fourth had clinically evident endocrine disease.

The potential clinical value of single or serial serum mucoprotein (M) determinations as an aid to differential diagnosis is discussed, with particular reference to patients with jaundice, hepatomegaly, and certain types of unresolved diagnostic problems.

The hypothesis has been presented that the mucoprotein (M) level at any one time in the patient represents a resultant or an equilibrium between two sets of factors: (1) hepatic and endocrine functions, which when impaired lower the M level, and (2) tissue proliferative and degenerative processes, which when accelerated, as in inflammatory, neoplastic, or traumatic disease, result in increased M levels.

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MEDIASTINAL TUMORS

A Survey of Modern Concepts in Diagnosis and Management

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WITHIN the confines of the mediastinum arise a heterogeneous group of tumors which, by reason of their peculiar derivation, their striking radiographic appearance, and their complex pathology, have long possessed a fascination far exceeding their incidence. Over the past 25 years, coincident with the advancement of thoracic surgery, these curious tumors have ceased to hold a purely academic interest and have assumed a more practical importance. Many reports have appeared stressing the hazards inherent in most mediastinal tumors and the minimal risk attending their excision. Yet, there somehow persists an unreasonable tendency to view them with complacency. In reviewing the records from three large hospitals of all patients with the diagnosis "mediastinal tumor" we repeatedly encountered patients in whom a radiographically demonstrable mediastinal mass had been inadequately investigated and therapeutically ignored. Since more and more of these tumors are being discovered in the asymptomatic stage as a result of x-ray surveys, it would seem that the danger of the allegedly benign mediastinal tumor need once again be reiterated, so that a more definite approach will be adopted toward the problem of the abnormal mediastinal shadow. In an effort to clarify these issues, a general discussion of mediastinal tumors seems justified, particularly with regard to the diagnosis and management of the primary mediastinal tumors.

Of fundamental importance in evaluating these tumors is their location in relation to the anteroposterior diameter of the chest. Since the usual anatomical divisions of the mediastinum have not, in our experience, provided any particular clinical advantage, we prefer a simplified division into superior and inferior mediastinal compartments, each with its anterior and posterior portions (Fig. 1). Such a division has ample clinical justification. The separation of the superior mediastinum aids in the differential diagnosis and choice of surgical approach. Since tumors of the anterior mediastinum often overlie the cardiac shadow, the middle mediastinum has been incorporated into the anterior mediastinum. One seldom sees tumors confined to the anatomical midmediastinum, and those which arise there, like bronchogenic

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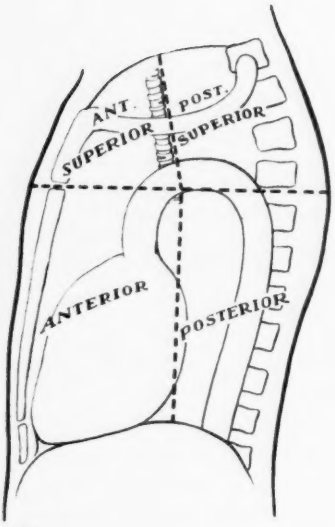

Fig. 1

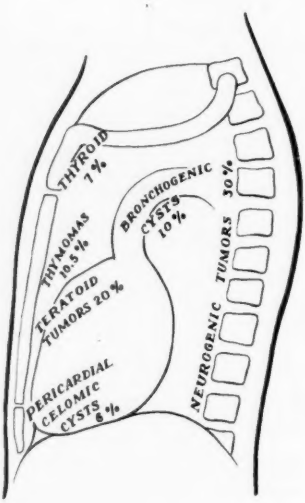

Fig. 2

Fig. 1.—Clinical divisions of the mediastinum.

Fig. 2.—Location and relative frequency of the commoner primary mediastinal tumors (after Brewer and Dolley [6]).

TABLE 1.—*Classification of Primary Mediastinal Tumors by Their Commonest Locations and Indication of Their Relative Incidence*

	%
Tumors of the anterior mediastinum	
Teratoid tumors	20.3
Thymomas	10.5
Intrathoracic thyroid adenomas	6.9
Pericardial celomic cysts	6.2
Lipomas	2.0
Lymphangiomas	1.3
Parathyroid adenomas	Very rare
Tumors of the posterior mediastinum	
Neurogenic tumors	30.6
Enterogenous cysts	1.1
Myxomas	Very rare
Xanthomas	Very rare
Intrathoracic meningoceles	Very rare
Plasma cell myelomas	Very rare
Chordomas	Very rare
Paratracheal tumors	
Tuberculomas	1.5
Tumors without strong anteroposterior location preference	
Bronchogenic cysts	9.9
Fibromas	3.7
Nonspecific cysts	3.4
Hemangiomas	1.7

TABLE 2.—*Relative Incidence of Primary Mediastinal Tumors Based on Reported Series*

Authors	Neurogenic Tumors *		Teratoid Tumors		Thymomas		Bronchogenic Cysts		Intrathoracic Thyroids		Pericardial Celomic Cysts		Fibromas		Nonspecific Cysts		Lipomas		Hemangiomas		Tuberculomas		Lymphangiomas		Enterogenous Cysts		Misc.	Total
	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M	
Blades	29	1	14	6	4	2	23	0	2	0	10	..	1	0	..	..	3	0	..	..	2	..	..	..	1	..	..	98
Curreri & Gale	6	1	11	1	1	1	2	0	3	0	2	..	..	..	..	..	1	0	..	..	..	..	1	..	1	..	..	31
Sellors	20	2	11		18		..	..	10		..	..	..	..	11	..	..	..	..	..	..	..	..	..	..	..	..	72
Harrington	48	3	34	6	8	0	10	0	5	0	7	..	5	6	8	..	1	0	5	5	3	..	3	..	4	..	..	161
Tiitinen	10	2	2	0	..	..	..	..	6	0	1	..	1	0	1	..	..	..	1	0	..	..	..	..	..	..	..	24
Brewer & Dolley	16	1	8	0	2	0	3	0	2	0	2	..	0	1	..	..	0	1	1	0	..	..	1	..	..	..	..	38
Santy, Berard, & Galy	18	5	11	2	1	1	8	0	..	..	4	..	2	..	..	..	..	..	..	..	2	..	..	..	..	..		54
Conklin	5	1	4	1	..	..	4	0	1	0	2	..	0	1	..	..	0	1	..	..	..	..	1	..	..	..	..	21
Hirschfeld	1	0	4	0	..	..	..	..	2	0	1	..	..	..	3	..	..	..	1	0	..	..	1	..	..	..	..	13
Samson & Dugan	14	1	8	0	4	1	6	1	4	0	2	..	..	..	..	..	1	0	..	..	4	..	1	..	..	..	1†	48
Lindskog & Kausel	7		6		2		7	0	2		4	..	..	..	..	..	..	..	..	..	..	..	2	..	..	..	1‡	31
Dotter & Steinberg	..	..	7	2	7	4	8	0	..	..	4	..	0	5	..	..	1	1	1	0	..	..	..	..	..	..	..	40
Shidler & Holman	15	0	1	0	2	2	2	0	3	0	2	..	0	1	..	..	..	..	..	..	..	..	..	..	..	..	..	28
Sabiston & Scott	15	5	8	4	12	5	5	0	4	1	2	..	1	0	5	..	2	0	..	..	..	..	..	..	2	..	2§	73
Burnett, Rosemond, & Bucher	11	7	8	2	1	2	1	0	9	1	6	..	2	4	1	..	2	0	..	..	2	..	1	..	2	..	1‖	72
	1		7		1																							
Peabody, Strug, & Rives	9	8	5	1	5	4	5	0	4	0	4	..	0	2	..	..	2	1	0	1	..	..	..	..	..	..	..	51
Total, benign vs. malignant	217	37	125	25	47	22	84	1	45	2	53	0	12	20	29	0	13	4	9	6	13	0	11	0	10	0	..	..
Total tumors	262 (30.6%)		174 (20.3%)		90 (10.5%)		85 (9.9%)		59 (6.9%)		53 (6.2%)		32 (3.7%)		29 (3.4%)		17 (2.0%)		15 (1.7%)		13 (1.5%)		11 (1.3%)		10 (1.1%)		5 (0.5%)	855

* B, benign; M, malignant.

† Intrathoracic meningocele.

‡ Thoracic duct cyst.

§ Parathyroid adenoma.

‖ Myxoma.

cysts, generally project either in a posterior or in an anterior direction. Metastatic tumors, granulomas, and lymphomas are exceptions to this rule. The paravertebral gutter, while not a part of the anatomical mediastinum, for clinical purposes has been included in the posterior mediastinum. The usual relationship of the commoner primary mediastinal tumors to the various mediastinal divisions is demonstrated in Figure 2.

It is essential to distinguish primary mediastinal tumors from other types, because as a rule they present distinct differences in management. The primary mediastinal tumors are listed in Table 1 according to their commoner locations. Their relative frequency has been arrived at by a summation of 855 unselected primary mediastinal tumors cited in various collected series* (Table 2). Several series are excluded, because they were presumably included in other reports.†

Various lesions have been excluded. Lymphomas, for example, are often classified as primary mediastinal tumors. While mediastinal involvement is fairly typical,

TABLE 3.—*Tumor Types Encountered in This Series*

Type	Tumors, No.	
	Benign	Malignant
Neurogenic tumors (17)		
Neurofibromas	7	..
Neurofibrosarcomas	..	6
Ganglioneuromas	2	..
Neuroblastomas	..	2
Thymomas (9)	5	4
Teratoid tumors (6)		
Cystic teratoids	4	..
Solid teratoids	1	1
Bronchogenic cysts (5)	5	..
Intrathoracic thyroid adenomas (4)	4	..
Pericardial celomic cysts (4)	4	..
Lipomas (3)	2	1
Fibromas (2)	..	2
Hemangiomas (1)	..	1
	34	17

it is usually but a part of a widespread process. For this reason, and because they present marked differences in management and prognosis, the lymphomas have in this study been arbitrarily excluded from the primary group. Also excluded are bronchogenic carcinoma; all metastatic malignant tumors; aneurysms and other cardiovascular abnormalities; tumors of the trachea and esophagus (other than bronchogenic and enterogenous cysts); tumors of the pleura, chest wall, and diaphragm; sarcoidosis; mediastinal abscesses, and hematomas. Until more is known about nonspecific carcinomas occasionally localized to the mediastinum, we consider it best to exclude them also. Many such carcinomas are probably of bronchogenic origin, although admittedly a few may arise in the thymus gland, teratoid tumors, etc. Although leiomyomas of the esophagus may be considered primary mediastinal tumors and not infrequently present as an asymptomatic mediastinal mass, we have nevertheless excluded them in an effort to obtain some uniformity of classification.

* References 1-15.

† References 16 and 17.

DIAGNOSIS

Clinical differentiation between the various primary mediastinal tumors is usually so uncertain that the diagnostic possibilities can seldom be reduced to a single one. Nevertheless, a familiarity with the features more or less characteristic of the individual tumors often proves valuable in narrowing the possibilities to a certain few. Each of these tumors will be discussed in detail, with frequent reference to our own series of 51 histologically proved primary mediastinal tumors (Table 3).

NEUROGENIC TUMORS

Of all primary mediastinal tumors the neurogenic tumors are the commonest, representing 30% of the cases in collected series.‡ Over one-third of our series are of neurogenic origin. They are of two types, those arising from nerve sheaths and those developing from sympathetic ganglion cells. Nerve sheath tumors include tumors originating from the outer sheath (neurilemomas) and a smaller group developing supposedly from the inner supportive sheaths (true neurofibromas). To avoid confusion we have included all nerve sheath tumors under the broad and more familiar designations, neurofibroma and neurofibrosarcoma. Sympathetic nerve cell tumors are referred to as ganglioneuromas. Those containing areas of malignant transformation are called ganglioneuroblastomas, while those which are poorly differentiated and frankly malignant are known as neuroblastomas (sympathicoblastomas).

Grossly, there is nothing to distinguish the neurofibroma from the ganglioneuroma other than the nerve trunk to which it is attached. Both are firm round tumors, well-encapsulated and often of considerable size. The tendency for multiple neurofibromas in von Recklinghausen's disease (neurofibromatosis) is well recognized. A rare but remarkable tendency of each is to present a dumbbell configuration, with bulbous mediastinal and intraspinal portions connected by an isthmus of tumor which traverses the intervertebral foramen. Both the neurofibroma and the ganglioneuroma are prone to malignant transformation, which has been reported in figures as high as 37%,[18] a figure which is considered much too high by many.§ This objection is substantiated by an analysis of unselected collected cases,‖ which shows 17% to be malignant. At any rate, the hazard of malignancy is considerable and becomes proportionately greater in patients with neurofibromatosis.

In general, neuroblastomas affect children; ganglioneuromas, adolescents and young adults, and neurofibromas, adults. The benign neurogenic tumors are often discovered by a chance x-ray. However, several authors ¶ have commented on the frequency with which these presumably asymptomatic patients will, upon close questioning, admit a vague and often bizarre type of interscapular pain. Of the many symptoms to which these tumors can give rise, pain is the most frequent and varies with the nerve involved. Specific nerve involvement is commonly encountered. Thus, a radicular type of intercostal neuralgia may accompany an intercostal neurofibroma, and Horner's syndrome, a ganglioneuroma. It should be emphasized

‡ References 1-15.
§ References 3, 5, 9, and 19.
‖ References 1-15.
¶ References 6 and 20.

that Horner's syndrome accompanying a neurogenic tumor must never be interpreted as evidence of inoperability. In one series of 48 intrathoracic neurogenic tumors [19] six were accompanied by Horner's syndrome, and only one of these proved malignant. Symptoms due to pulmonary or esophageal compression are not infrequent, and signs of extramedullary spinal cord compression generally accompany the dumbbell tumors. Rapidly progressive signs and symptoms suggest malignant transformation.

Symptoms were the rule in our patients, being absent in only 5 of the 17. Chest pain predominated and was often bizarre. Cough, dyspnea, and dysphagia occurred with both benign and malignant cases, but were usually severer in the malignant ones. In two patients the initial complaint was scoliosis. One developed a marked curvature with great rapidity and proved to have a neurofibrosarcoma. The other wore a brace for eight years before a neurofibroma became visible on x-ray.

Radiographically, the appearance of neurogenic tumors is classic. Any round well-demarcated nonpulsatile lesion situated far posteriorly in the paravertebral gutter is a neurogenic tumor until proved otherwise. In a review of 100 such tumors Hirschfeld [9] found 77 to lie in the superior mediastinum. Erosion of vertebrae or ribs with or without associated scoliosis may result from benign pressure or malignant invasion, but ragged bone destruction indicates malignancy. Dumbbell tumors usually show widening of an intervertebral foramen. Calcification is more common in the ganglioneuromas.

On the basis of their progressive growth and malignant tendency, all neurogenic tumors should be excised. All of the nine benign lesions in our series were excised without incident. Three of the eight malignant tumors were also completely resectable, and the patients are alive and well today. The remainder were either inoperable or partially unresectable, and the patients are presumably dead.

TERATOID TUMORS

That a close affinity exists between dermoid cysts and teratomas is reflected in the frequency with which teratomatous elements can be demonstrated in the walls of dermoid cysts. Hence, they are best referred to collectively as teratoid tumors or as cystic and solid teratomas. Due to their extraordinary morphology, teratoid tumors are the most frequently reported mediastinal tumors and were once regarded as the commonest. Actually, from our studies # we have found that they comprise 20% of all primary mediastinal tumors.

These tumors probably result from embryologic maldevelopment within the branchial clefts in the vicinity of the thymus anlage, the pericardial celom, and the great vessels, with which they later descend into the chest and to which they often show attachments. They occur almost exclusively in the anterior mediastinum, being found at any level but most frequently at the base of the heart.

The cystic teratomas outnumber the solid and are usually unilocular and filled with a thick grumous fluid containing sebaceous material and hair. Islands of teratomatous tissue, sometimes including a tooth or bone, project from the lining epithelium. The solid teratomas are more complex. They may contain well-differentiated tissue from almost any organ thrown together in a weird disorganized con-

References 1-15.

glomeration. Both types, but especially the solid, show a highly significant tendency to become malignant. The figure generally quoted is 12%.* A more reliable estimate, obtained from collected unselected cases,† is that 20% are malignant. Out of the seemingly endless variety of tissues present, malignancy of almost any cell type may develop. On rare occasions, chorioepitheliomas, embryonal carcinomas, and seminomas identical with those of the testes may represent primary mediastinal tumors,[23] providing meticulously examined multiple histological sections of the testes disclose no primary lesion nor a suggestive scar. One such case, a seminoma, is included in this series.

Unless infection or malignant transformation intervenes, mediastinal teratoids usually do not give rise to symptoms until the third or fourth decades of life. Symptoms do eventually occur in virtually every case, the commonest being cough and anterior chest pain. Dyspnea or actual stridor may occur, sometimes only when the patient is lying supine and the tumor falls back upon the trachea. The expectoration of hair may provide pathognomonic evidence of a cystic teratoid, but this has occurred in only 10% of the cases reviewed by Rusby [21] and in only five of 100 subsequent cases of cystic teratoid tumors which we have reviewed. Occasionally cystic teratoids may become secondarily infected and give rise to severe symptoms, but, in general, rapidly progressive symptoms are indicative of malignancy. Obstruction of the superior vena cava commonly occurs with malignant teratoids, seldom with benign ones. Gynecomastia and a positive Ascheim-Zondek test may accompany a mediastinal chorioepithelioma.

The radiographic picture is typically that of a round or oval sharply-defined unilateral shadow confined to the anterior mediastinum. The mass may be of homogeneous density, but teeth, bone, or bits of calcium are not infrequent. The wall of cystic teratomas may be completely calcified, as it was in one of our cases.

Since symptoms eventually arise in practically every case and 20% of the tumors are or will become malignant, there can be no question about the advisability of operation. All five benign teratoids of this series were accompanied by symptoms, and all were completely excised without incident. One occurred in a four-month-old infant, who, insofar as we know, is the second ‡ youngest child on whom resection has been successfully performed.[24]

THYMOMAS

On the basis of collected unselected cases,§ thymomas represent 10.5% of all primary mediastinal tumors. They are consistently confined to the anterior mediastinum, being most commonly situated anterior to the base of the heart and the aortic arch. They may occur anywhere between the retromanubrial area and the cardiophrenic angle.

For our purposes all thymic tumors have been grouped under the noncommittal term, thymoma. Most are encapsulated ovoid tumors containing multiple small cystic spaces. Calcification is common. Some show invasion of the capsule, with

* References 21 and 22.

† References 1-15.

‡ The case of another infant, 2 months of age, from whom a solid teratoma was successfully excised has subsequently been reported (Gross, R. E.: The Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1953).

§ References 1-15.

extension to contiguous structures. Three thymomas from our group illustrate the gross peculiarities which may mask the true identity of these tumors. In one the cystic element so dominated the picture that minimal thymic tissue remained—the so-called thymic cyst.[25] In another the cystic spaces were equally prominent but were filled with putty-like material. This tumor, as so frequently is the case,[11] was initially mistaken for a tuberculoma, which it may simulate both in appearance and in location. The third tumor appeared obviously lipomatous, and its origin was only ascertained histologically (lipothymoma ‖).

The incidence of malignancy among thymomas is known to be high, as manifested by 20% being malignant in one series [28] and 24% in another.[29] In our analysis of unselected cases 32% were malignant.¶ To determine histologically the malignancy of certain thymomas may be impossible and may have to await evidence of invasion, pleural seeding, or recurrence. Distant metastases are practically unheard of and militate against a diagnosis of thymoma.

Benign thymomas are generally asymptomatic and discovered by chance. A significant number, generally more than the one to five ratio in our series, are associated with myasthenia gravis. In malignant thymomas anterior chest pain, dyspnea, and superior vena cava obstruction are apt to occur; each is a poor prognostic sign. Initially, none of the five patients of this series with benign thymomas had symptoms relative to the tumor. By contrast, each of the four patients with malignant thymomas complained of dyspnea; three complained of anterior chest pain, and two presented a superior vena cava syndrome.

Thymomas have no radiographic features which distinguish them from other anterior mediastinal tumors. They are usually round or ovoid and present a sharply marginated border. Occasionally they may not be visible except on lateral view. Calcium is often visible in the malignant as well as in the benign thymomas. The presence of an anterior mediastinal tumor in a patient with myasthenia gravis is justifiable grounds for a diagnosis of mediastinal thymoma.

The high potentiality of malignancy of both thymomas and teratoid tumors renders surgical excision mandatory in every indeterminate anterior mediastinal tumor. In cases of myasthenia gravis in combination with a thymoma, excision of the tumor is performed not in an effort to improve the myasthenia but because of the tumor per se. The five benign thymomas of this series were resected without a fatality. Of the four patients with malignant thymomas, two were greatly benefitted by a combination of surgical excision and postoperative irradiation.

BRONCHOGENIC CYSTS

Bronchogenic cysts are congenital cysts arising as an embryologic diverticulum from either the foregut or its tracheal bud. An analysis of collected unselected cases # discloses that these cysts represent 10% of primary mediastinal tumors, ranking close behind thymomas in relative frequency. Although they usually originate in the region of the carina, they eventually project into the posterior or, somewhat less frequently, into the anterior mediastinum. Most typically they are found at the approximate level of the aortic arch, but they have been described high in the superior and low in the inferior mediastinum.

‖ References 26 and 27.

¶ References 1-15.

References 1-15.

They are round or ovoid, typically thin-walled, occasionally multilocular cysts, containing a fluid that may be clear or a turbid white and is occasionally gelatinous. Within the cyst wall one finds tissue comparable to that of the bronchus, including a pseudostratified ciliated columnar epithelium. When the wall contains only connective tissue and no cartilage, smooth muscle, or mucous glands and when the epithelium is cuboidal or stratified squamous rather than ciliated columnar, the diagnosis may be equivocal. Some of the nonspecific cysts described in the literature undoubtedly represent bronchogenic cysts of this type. In such a situation, a fibrous connection with the tracheobronchial tree may lend assurance to the diagnosis. When the question of cystic teratoids of the posterior mediastinum is investigated, some appear to have been bronchogenic cysts in which the tissue elements were interpreted as teratomatous instead of bronchial. Recently the interesting observation has been made that these cysts are often associated with cystic disease of a lesser extent within the lungs.[30] Although a tendency to malignant change might be suspected from their embryogenesis,[1] very few proved cases of carcinomatous * or sarcomatous [32] transformation have been reported. They grow very slowly, but occasionally one will become infected and exhibit rapid enlargement.

In children bronchogenic cysts are especially apt to produce severe symptoms, as illustrated by two patients in our series who had repeated episodes of severe dyspnea and cyanosis and who eventually died of obstructive pneumonitis, without surgical consultation. Bronchogenic cysts in adults are often discovered by routine roentgenograms, but as the patient grows older symptoms do tend to occur. Chest pain has long been cited as the main symptom in these patients, but in our experience and from a review of the literature we gain the impression that tracheal symptoms are considerably commoner. All three adults with bronchogenic cysts in this series presented identical symptoms of cough, dyspnea, and a choking sensation.

In the roentgenogram bronchogenic cysts generally present a spherical or ovoid smooth-bordered density in the posterior mediastinum near the tracheal bifurcation. A substantial number occur anteriorly, and, like so many other primary mediastinal tumors, they may be seen anywhere between the superior mediastinum and the cardiophrenic angle. The mass may have a demonstrable tracheal or bronchial attachment, which is best demonstrated at fluoroscopy by a rise and fall with deglutition. Radiographic evidence of calcification is unusual.

Although bronchogenic cysts are not without danger, the chief reason for routinely advising their surgical excision is the impossibility of ruling out a more menacing tumor.

INTRATHORACIC THYROID TUMORS

In this discussion the term intrathoracic thyroid applies solely to totally intrathoracic thyroid tissue having a limited or no connection with the thyroid gland proper. It seems likely that the majority of these lesions develop from a nodular cervical thyroid with subsequent descent into the chest. A few, however, probably represent embryologic aberration.

Among collected unselected cases 6.9% of primary mediastinal tumors were intrathoracic thyroid goiters.† In 1947, one of us (J. D. R.) reported three cases of completely intrathoracic goiters, one of which was posterior in location.[33] In all

* References 10 and 31.

† References 1-15.

probability, neither the intrathoracic goiter nor its posterior component is as rare as was once thought, for we are aware of at least 55 posterior mediastinal goiters referred to since then.

These tumors are discrete round or lobulated masses, differing in no respect from thyroid adenomas of the neck. They generally prove to be nodular goiters; uncommonly there are adenocarcinomas, and on only one occasion was a Hürthle-cell tumor found.[34] The risk of carcinomatous transformation should presumably be the same as for nodular goiter of the neck. A connection with the thyroid gland can often be delineated, but it is occasionally no more than a thin fibrous band.

Approximately one-half of these patients have no symptoms referable to the mediastinal tumor. Three-fourths of these tumors occur in middle-aged women, most of whom give a history of a previous thyroidectomy or present evidence of an enlarged cervical thyroid gland. Symptoms usually stem from pressure on the trachea. The two most frequent symptoms are dyspnea, which is often described as a choking sensation intensified by the supine position or by turning the head to the side of the tumor, and a brassy, irritative cough. Occasionally these patients complain of hoarseness or a wheeze. With anterior tumors retrosternal discomfort is not infrequent, while posterior tumors may produce dysphagia. Evidence of mild toxicity is not uncommon. Like other anterior mediastinal tumors, they can give rise to superior vena cava obstruction. Three of our four patients had symptoms, in two due to tracheal and in one, esophageal compression.

The typical radiographic picture is that of a high anterior mediastinal mass projecting, in by far the majority of cases, from the right mediastinal border. In rare cases these tumors may actually rest on the diaphragm.‡ That they may also occur posteriorly has already been emphasized. Toxic goiters in general do not tend to visualize as well radiographically as the nontoxic ones, and they may be missed on multiple views of the chest. This is apparently due to the decreased density of the toxic thyroid, which permits it to blend with other mediastinal structures.[37] Deflection of the trachea and upward motion of the tumor on swallowing are extremely valuable presumptive signs. Calcification is radiographically demonstrable in somewhat over 25% of cases but cannot be differentiated from that occurring with other mediastinal tumors. Many posterior thyroid tumors produce a compression or displacement of the esophagus. In a middle-aged thyroidectomized woman with a right superior mediastinal tumor which displaces the trachea and moves upward on swallowing, the diagnosis of an intrathoracic goiter would be practically assured.

Surgical excision of these tumors would seem advisable for several reasons. Mild degrees of tracheal compression are often progressive, and acute obstruction may result from incarceration of the tumor in the superior thoracic strait. The danger of malignancy is significant, and it is sometimes difficult to rule out a more highly malignant tumor, such as a thymoma or a solid teratoma.

The surgical approach to these tumors is variable. High anterior mediastinal tumors with an associated nodular goiter in the neck should undoubtedly be removed by a cervical approach, for they are encapsulated and their blood supply is usually quite accessible. When it is excessively large, the tumor can be safely excised by morcellation. However, if excision cannot be accomplished solely by the cervical

‡ References 35 and 36.

route we prefer a transpleural approach. Intrathoracic thyroid tumors unassociated with a cervical goiter are likewise best resected transpleurally, since an anomalous blood supply is not unusual. Of our three operated cases, in two the tumors were excised through the chest and both derived their blood supply from anomalous sources, one from the aorta and one from the subclavian artery. We are convinced that any attempt to excise these tumors through a cervical approach would have proved foolhardy and probably fatal.

Patients in whom surgery is contraindicated may be considerably aided by radioactive iodine. One of the patients in this series presented a retrotracheal nodule producing mild respiratory symptoms. The presumptive diagnosis of an intrathoracic thyroid adenoma was proved by I^{131} studies. Because the patient was considered a poor surgical risk, he was treated with radioactive iodine, and complete symptomatic relief ensued.

PERICARDIAL CELOMIC CYSTS

As the term implies, pericardial celomic cysts are generally thought to arise embryologically from a failure of one of the primitive disconnected lacunae to merge with the others as it normally would do in forming the pericardial celom. Some prefer to incriminate the pleuropericardial membrane.

These cysts were considered rare a few years ago, but it has become apparent that they are not too uncommon. Pericardial celomic cysts comprised 6.2% of all collected series cases which we analyzed.§ Over 90% occupy a classic location in the anterior cardiophrenic angle, usually on the right. They may lie in a supracardiac position, and rarely they occur posteriorly. One of our four pericardial celomic cysts lay posterior to and to the left of the heart.

Pericardial celomic cysts are spherical and usually unilocular cysts with a thin transparent wall containing a clear, colorless, or amber fluid. They are usually attached to the pericardium. Microscopically they consist of an acellular fibrous wall having an endothelial-lined inner surface. Pathological distinction between these cysts and the multilocular lymphangiomas arising in the same location may be impossible.

These cysts are notorious for their lack of symptomatology, but in a recent review [38] attention was called to the fact that mild symptoms, consisting primarily of pain in the precordium, shoulder, or epigastrium, do occur in approximately two-thirds of these patients. Dyspnea, cough, palpitation, tachycardia, and dysphagia have also been noted. None of our four cases presented symptoms, however.

The x-ray appearance of these lesions is distinctive but not diagnostic. They are round or oval shadows with a sharp border, situated in the anterior cardiophrenic angle. They are of uniform density and cannot be separated from the pericardium even with a pneumothorax. It is important to demonstrate, by positioning the patient, that the cyst does not empty into the pericardium, for a pericardial diverticulum would not warrant surgery. A pneumoperitoneum may be helpful in ruling out a foramen of Morgagni hernia. Aspiration of clear fluid from an anterior cardiophrenic angle tumor is probably diagnostic, and it has been suggested that such a finding justifies conservative management.[15] Since many potentially malignant tumors may lie in this location, we prefer not to attempt aspiration but advocate surgical excision. All four of our patients were operated upon without a fatality.

§ References 1-15.

MESENCHYMAL TUMORS

Fibromas.—About 4% of all primary mediastinal tumors are fibromas and fibrosarcomas. In all likelihood the declining number of fibromas is due to the fact that a neurogenous element was not recognized in some of the older neurogenic tumors. The fibromas, though slow growing, may attain tremendous size. Symptoms generally appear late. Their radiographic appearance and location are of no diagnostic value. Uncertainty as to the diagnosis invariably warrants surgery; their steady growth justifies it. The fibrosarcomas outnumbered the fibromas in collected series cases, and, again, this probably represents a greater difficulty in recognizing the nervous element in malignant nerve tumors. A large fibrosarcoma of the anterior mediastinum was the only tumor of this type among our cases. Although it presented a circumscribed oval appearance on x-ray, it was unresectable.

Lipomas.—Mediastinal lipomas are quite rare, constituting only 2% of primary mediastinal tumors. They are predominantly anterior and more often inferior in location, and eventually they may attain gigantic proportions. Some present a palpable cervical or thoracic wall extension, which may give a dumbbell appearance. Symptoms eventually occur in most cases and vary with the location of the tumor. The radiographic appearance is usually that of a round bossellated mass in which it is sometimes possible to discern a central density and a less opaque periphery. They are occasionally mistaken for an empyema and may transmit a boggy sensation upon attempts at aspiration. A malignant change is practically unheard of, most of the very rare liposarcomas probably having been malignant from the start. Surgical excision is always indicated, owing to the progressive and frequently indeterminate nature of the lesion.

Three symptom-producing lipomatous tumors were encountered in this series. One lipoma presented in the anterior superior mediastinum and another in the right anterior cardiophrenic angle. Both were easily excised. The third was an autopsied case in which a liposarcoma filled the entire mediastinum.

Myxomas and Xanthomas.—These tumors are exceedingly rare. The customary position of xanthomas in the paravertebral gutter suggests that at least some are neurofibromas containing large numbers of lipophages.[39] The myxomas may likewise represent degenerative forms of mesenchymal and neurogenic tumors.

VASCULAR TUMORS

Hemangiomas.—These are rare mediastinal tumors. They present a cystic vascular appearance, and about half are malignant hemangioendotheliomas. Symptoms, though variable, are frequently severe. Surgical excision is obviously the treatment of choice, for many benign and more than a few malignant tumors of this sort are resectable. The one vascular tumor of this series was a posterior hemangioendothelioma that was thought to have been completely excised.

Several hemangiopericytomas || and one glomus tumor [41] have also been reported in the mediastinum.

GRANULOMATOUS TUMORS

Tuberculomas.—So-called tuberculomas of the mediastinum have rarely been reported. They are granulomatous lesions whose relationship to tuberculosis, while logical, is largely presumptive, since acid-fast stains are usually negative. They

|| References 12 and 40.

are solitary round or oval uniformly-dense mediastinal lesions occupying a fairly constant location in the right paratracheal region at or slightly above the level of the aortic knob. It should be stressed that they are indeterminate lesions and are distinctly different in appearance from obviously tuberculous nodes, which, though similar in location, are often calcified, usually multiple, and commonly bilateral.[42] Symptoms accompany about half of these lesions and are generally related to their intimate relationship to the trachea. Because of uncertainty as to the precise diagnosis, surgery seems justified.

LYMPHANGIOMAS

Lymphangiomas of the mediastinum are distinctly rare. They comprised only 1.3% of collected unselected cases,¶ and we encountered no cysts of this sort in our own series. They are multicystic structures filled with thin clear fluid. A few are densely adherent to surrounding structures, suggesting that they are aberrant cystic hygromas. Often they are well circumscribed and possibly arise from pericardial lymphatics. Schlumberger [25] has suggested that some may be related to involutional changes in the thymus, and several case reports seem to bear out his contention.[43] The cystic spaces are lined by flattened endothelial cells, and within the thin fibrous walls can be seen aggregates of lymphoid cells, smooth muscle, blood vessels, and nerves. Their multicystic appearance and the presence of lymphocytes and muscle are the features of importance in distingishing them from pericardial celomic cysts.

They are characteristically asymptomatic. Unlike the cystic hygromas of the neck, they are found usually in adults, often by routine roentgenography. When symptoms are present, they are likely to be respiratory and may be severe. The radiographic appearance of these tumors is usually that of an ovoid or lobulated shadow with well-defined borders and a homogeneous density. They occur anteriorly and are prone to involve the inferior portion of the anterior mediastinum on the right side, so that by both location and histology they are apt to be confused with pericardial celomic cysts.

Because of their clinically indeterminate nature, all should be excised.

ENTEROGENOUS CYSTS

Enterogenous cysts, like bronchogenic cysts, are believed to originate as diverticula of the primitive foregut, but they may arise by a failure of coalescence of the vacuoles which usually combine to form the lumen of the primitive gut. They are exceedingly rare, as indicated by there being only 10 among the 855 primary mediastinal tumors in the various series we have analyzed.# None were encountered in our series. They commonly show an attachment to the esophagus and may actually lie within the wall of the esophagus. They are lined most frequently with gastric mucosa, less often with enteric or esophageal epithelium, and rarely with bronchial epithelium. A few rare instances have been reported in which tubular duplication cysts originated in small bowel and projected through the diaphragm into the mediastinum.*

Since the mucosa which lines these cysts is frequently active, they usually cause symptoms in infancy or early childhood. Symptoms of tracheal compression are frequent and often violent. Peptic ulceration and hemorrhage are not infrequent,

¶ References 1-15.

References 1-15.

* References 44 and 45.

and in cysts with a patent communication with the esophagus hematemesis and melena may occur. Inactive cysts may remain unobtrusive until adulthood and be picked up only by a routine chest x-ray. Their extreme rarity in adults is due in part to their lethal tendency in children. On x-ray these tumors appear spherical when small or as elongated, ovoid structures when large. They lie posteriorly and almost invariably extend to the right, probably because of the aortic barrier. Esophageal compression or intercommunication may be demonstrable on barium swallow. Occasionally one of these cysts will undergo malignant transformation.[46] Surgical excision is exigent. In poor-risk patients these cysts may be handled by initial marsupialization and subsequent extirpation.

INTRATHORACIC MENINGOCELE

These tumors, as indicated by reports of only 17 cases, are quite rare. They are frequently associated with von Recklinghausen's disease, and this coupled with their location in the paravertebral gutter, with frequently associated spinal deformity and rib erosion, leads in most instances to a preoperative diagnosis of neurofibroma. Myelography or aspiration may be diagnostic. When the diagnosis can be established clinically, surgery may not be indicated for the asymptomatic patient. With large or symptom-producing lesions, surgical excision seems warranted. We have had no personal experience with these lesions.

PARATHYROID ADENOMAS

Parathyroid adenomas rarely enter into the differential diagnosis of radiographic abnormalities of the mediastinal shadow and will therefore receive only passing comment. With exceedingly rare exceptions,† they never present primarily as a mediastinal tumor. In reviewing 322 parthyroid adenomas, Norris [49] found only 6.8% within the mediastinum, most being anterosuperior in location and accessible through a cervical incision. Occasionally they occur within the thymus. No parathyroid adenomas of the mediastinum have been included in our series.

MISCELLANEOUS TUMORS

There have appeared isolated reports of several rare tumors presenting primarily as a mediastinal mass. These include paragangliomas, both the hormonally inactive [39] and the hormonally active (pheochromocytoma),‡ chemodectomas,§ chordoma,[54] plasma cell myeloma,[55] and thoracic-duct cyst.[56]

VARIOUS DIAGNOSTIC AIDS

History.—In the unsuspected mediastinal tumor a careful history with attention to vague and supposedly bizarre complaints may prompt an x-ray and thereby discover the tumor. However, the signs and symptoms produced by a mediastinal tumor seldom provide a clue to the particular type of tumor one is dealing with. Exceptions to this rule do exist and should not be overlooked in the history. The expectoration of hair, mild degrees of myasthenia gravis, a previous thyroidectomy or symptoms of hyperthyroidism, a history of syphilis, and intermittent attacks of dizziness and sweating may suggest the nature of the lesion.

† References 47 and 48.

‡ References 50 and 51.

§ References 52 and 53.

Physical Examination.—A search for palpable lymph nodes, an enlarged thyroid, the stigmata of von Recklinghausen's disease, a lipoma of the chest wall overlying the tumor, scoliosis, Horner's syndrome, signs of spinal cord compression, a testicular nodule, or gynecomastia may serve to pigeon-hole the diagnosis.

X-Ray.—As we have repeatedly stressed, the chief lead to the correct diagnosis of any given mediastinal mass is its radiographic location, particularly its relationship to the anteroposterior diameter of the chest. The size, shape, and relative density of the tumor may be of some significance, as may a fluid level, presence of a tooth or bone, vertebral erosion, or widening of an intervertebral foramen. Planigrams are of value in demonstrating teeth, bone, or calcium and in showing an attachment or close relationship to some adjacent structure. Fluoroscopy will often prove misleading in distinguishing between inherent and transmitted pulsations but is of particular value in demonstrating a paralyzed hemidiaphragm, movement of the mass with deglutition, or the cystic nature of a tumor evidenced by a change in size with the Mueller and Valsalva maneuvers. A barium swallow may reveal an intrinsic esophageal mass, the presence of external esophageal compression, or a megaesophagus or may fill an enterogenous cyst. A barium enema is essential in right paracardiac shadows, since a foramen of Morgagni hernia usually occupies that position, and may be best approached transabdominally. Even if the hernia contains nothing but omentum, a characteristic distortion of the transverse colon may be noted. Pneumoperitoneum may also demonstrate such a hernia, while pneumothorax may be helpful in establishing the extrapulmonary location and diaphragmatic or pericardial attachment of a mass. A myelogram is helpful in dumbbell tumors and meningoceles.

Angiocardiography has greatly improved the diagnostic accuracy of mediastinal tumors in the vicinity of the arch of the aorta, innominate artery, or descending aorta. We recently saw a patient with a round 5 cm. lesion in the left paravertebral gutter which appeared to be a typical neurofibroma. Angiocardiography proved it to be a saccular aneurysm and thus permitted a planned surgical approach.

Radioactive Iodine.—Many but not all intrathoracic thyroid tumors pick up quantities of radioactive iodine sufficient to plot out their location by tracer technique. Moreover, a therapeutic course of radioactive iodine, although justified only in the poor-risk patient, may provide equally sound diagnostic proof in the form of decreased tumor size or relief of tracheal compression.

Diagnostic Irradiation.—In the management of mediastinal tumors the question as to whether test irradiation should ever be used and, if so, when, has never been completely settled. A growing number of roentgenologists now refuse to employ radiotherapy without histological verification of the tumor type. Surgeons in general are still more adamant in condemning this procedure. We personally feel that test irradiation has a definite though limited field of usefulness when applied to large lobulated anterior or midmediastinal masses centered at the level of the carina with equal projection into both hemithoraces. The vast majority of such cases are unresectable lymphomas. If within two to three weeks after a test dose of irradiation (500 to 1000 r) marked regression in size of the mass is not noted, we promptly explore these patients. There is some evidence that in a number of lymphomas there is a better chance for cure with a combination of surgery and

radiotherapy than with irradiation alone.|| We feel very strongly that patients presenting definite lateralization of the mass are not candidates for diagnostic irradiation.

Biopsy.—When a lymphoma is suspected, significant palpable lymph nodes should carefully be searched for and biopsy done. When one of the granulomatous diseases is suspected, scalene node biopsy and needle biopsy of the liver may occasionally provide a diagnosis and obviate needless surgery. Bronchoscopy with or without biopsy is chiefly of value in excluding a central type of bronchogenic carcinoma. We have not attempted needle biopsies of the mass itself, and we do not advocate use of this procedure, since the complications from an exploratory thoracotomy are probably no greater, representative tissue can be assured, and excision, which will probably be indicated anyway, can be simultaneously accomplished.

MANAGEMENT

Despite all these diagnostic procedures, most of these lesions still cannot be diagnosed with certainty. The most distressing feature is that, when this impasse is reached, all too often the incorrect decision is apt to be made. The physician who inteprets a lack of symptoms, an apparent absence of growth, or the presence of calcification in a sharply circumscribed mediastinal tumor as evidence of an innocuous lesion is ill-acquainted with the sinister inclinations of these tumors. Where else in the body could a large mass appear and conservative treatment be advised? Of all tumors in the collected series 13.7% were stated to be malignant and many others were malignant in location, if not in histology.¶ To embark on a program of watchful waiting is to invite disaster. No better example of the fallacy in this attitude can be cited than a patient reported by Maier,[60] who presented a round calcified anterior mediastinal tumor which for four years had been observed without any change in size. When it did begin to enlarge thoracotomy was advised, but, unfortunately, the patient was found to have a highly malignant undifferentiated carcinoma arising in and extending through the wall of a cystic teratoma. Excision was precluded by mediastinal and hilar infiltration. There is little question but that an exploration four years previously would probably have proved life saving. Such instances are by no means limited to this one case and serve to emphasize that a policy of conservatism often forsakes the chance for cure.

Equally important in the decision to operate is the ease with which excision can be effected in the benign uncomplicated case. No deaths occurred in our group of 31 benign resected mediastinal tumors. Of 532 benign resected cases from collected series the mortality rate was 2.8%, and there were several series in addition to our own in which no deaths occurred in resections of benign lesions.# Great stress should be placed on the extremely low mortality among young adults. If surgery is postponed in these persons, even though the tumor may not become malignant, the risk with surgery will be proportionately greater as their age increases.

Among the malignant tumors the operative mortality is greater and the salvage rate less, but it is true, nevertheless, that a significant number can be cured. Of 13 malignant tumors from our own series which were explored, eight proved incom-

|| References 57-59.

¶ References 1-15.

References 1, 6, and 8.

pletely resectable. One of these patients died on the ninth postoperative day, and, although he appeared to have died from progression of his already advanced disease, he has been classified as the sole surgical death in this series. The tumors in the five remaining patients were all thought to have been completely resected. There were no fatalities. All have remained well to date, but the follow-up in three is too brief to be conclusive. Certainly the results tend to refute the view that surgery is either excessively hazardous or ineffectual.

When confronted, therefore, with the problem of a mediastinal tumor which remains indeterminate, as so many do, following a diagnostic evaluation, exploratory thoracotomy would then seem mandatory. In fact, so costly may be the diagnostic workup, so frequent the need for surgery even at the end of extensive studies, and so slight the operative risk, that considerable judgment must be exercised in selecting only those diagnostic procedures which may materially influence the choice of therapy.

SUMMARY

Primary mediastinal tumors can usually be differentiated from other lesions of the mediastinum with the aid of modern diagnostic methods. The clinical and radiographic features of each type of primary tumor are discussed in detail; they are often found to be distinctive but are seldom diagnostic.

An analysis of 855 unselected primary mediastinal tumors, including 51 cases of our own, lends added weight to the evidence already in the literature attesting to the danger inherent in these tumors. Of the entire group at least 13.7% were histologically malignant, and many others were malignant by size or position.

Any claim that surgery is overly hazardous or necessarily futile is refuted by the results in our series. Among the benign resected tumors there were no fatalities, while among the malignant tumors there was a considerable salvage.

We conclude that irrespective of the presence or absence of symptoms, conservatism has no place in the management of the indeterminate mediastinal tumor. Prompt recourse to exploratory thoracotomy not only obviates the loss of valuable time and expense but also constitutes the safest approach to this problem.

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MASS ORAL PENICILLIN PROPHYLAXIS IN CONTROL OF STREPTOCOCCAL DISEASE

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IN A RECENT publication [1] Wannamaker and his colleagues demonstrated that the incidence of Group A Streptococcus carriers and disease rates could be lowered significantly by the mass oral administration of penicillin in two daily doses of 500,000 or 1,000,000 units each, provided that such treatment was maintained for 10 days. When the penicillin was administered for shorter periods of time or when single daily doses of 250,000 units were used, the resultant prophylactic effect was inadequate.

The observations which form the basis for this report describe two separate field trials which were conducted among Air Force recruits at Sampson Air Force Base at a time when there existed hyperendemic conditions of streptococcal disease. These trials are part of a larger project [2] conducted under the auspices of the Department of Preventive Medicine of the Air Force and The School of Aviation Medicine, but they are being reported separately at this time because they seem to supply an answer for an important question which was raised by Wannamaker and his colleagues [1]; namely, whether 250,000 units of orally administered penicillin twice daily for 10 days would prove effective in the control of Group A streptococcic disease and carriers. A detailed review of the literature will not be presented here, since this has been done by Wannamaker.[1]

METHODS AND MATERIALS

The physical arrangement of Sampson Air Force Base is such as to permit its recruit personnel to be divided readily into two areas of approximately equal strengths and training schedules (Troops I and II), with very limited opportunities for intermingling. New arrivals

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at the base are assigned to each area in similar numbers and rates. The studies reported here were conducted in January, 1953, and in April, 1953. In the first field trial, Troop II (approximately 5,500 men) received 250,000 units of penicillin twice daily for 10 days, while a similar number of recruits (Troop I) served as untreated controls. In April, 1953, the entire personnel of both troops and their permanent parties, approximately 19,000 men, received penicillin in the same schedule, except that all new men subsequently reporting to Troop II continued to receive similar treatment while those reporting to Troop I were not treated. The penicillin was administered orally either one hour before or two hours after breakfast and again at bedtime.

All personnel admitted to the hospital because of respiratory disease during the observation periods were examined for the presence of exudative pharyngitis and, in addition, had pharyngeal cultures taken for beta-hemolytic streptococci. Weekly carrier surveys were made by obtaining pharyngeal cultures from 15% of both the study and control populations during the same periods. These were made by swabbing the pharynx and tonsillar regions with warm, dry, sterile cotton swabs from which sheep's blood agar plates were immediately inoculated.

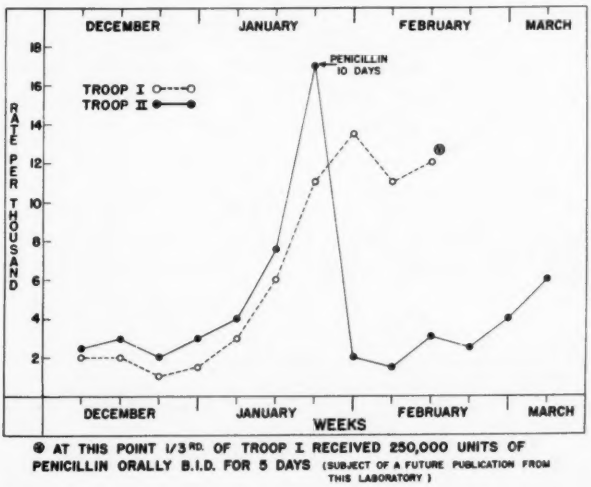

Fig. 1.—Effects of penicillin by mouth, 250,000 units twice daily for 10 days, upon a streptococcal disease epidemic in a recruit population.

Streptococci exhibiting beta hemolysis were grouped and typed * by the methods of Maxted [3] and Swift, Wilson, and Lancefield.[4] During the respiratory disease season of 1952-1953, Type 3 was the prevalent Streptococcus at this military base, with Types 12, 42, and 28 next most frequent.

DATA

A. *Oral Penicillin Prophylaxis Administered to Troop II for a Ten-Day Period (Fig. 1).*—During the third week of January, 1953, the Group A Streptococcus disease rates were 13 per 1,000 per week in Troop I and 17 per 1,000 per week in Troop II. Penicillin prophylaxis was instituted for 10 days to all Troop II recruits and associated permanent party members in the manner which has already been described. Hospital admissions for streptococcal disease diminished sharply within

* The streptococcal grouping and typing sera were obtained from the Communicable Disease Center, Chamblee, Ga., through the efforts of Dr. Elaine Updyke. Sera for Types 1-6, 11-15, 17-19, 22-24, 26-33, 36-44, 46, and 47 were available for this study.

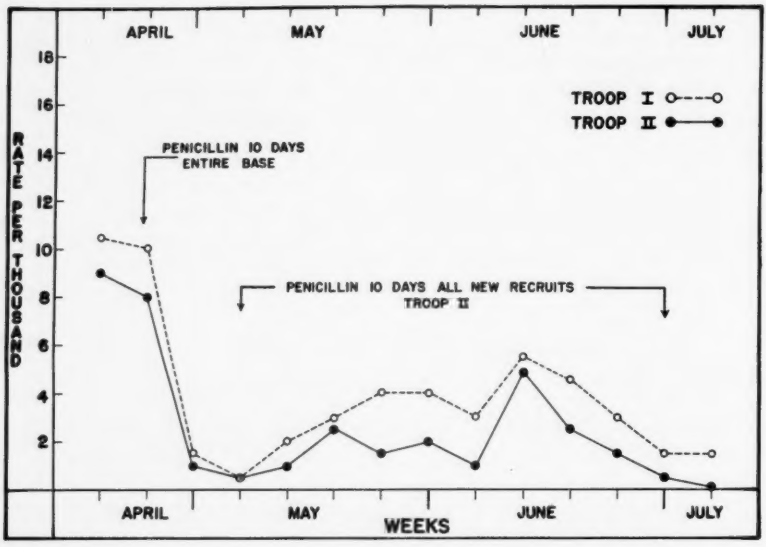

Fig. 2.—Effect of penicillin by mouth, 250,000 units twice daily for 10 days, upon a streptococcal disease epidemic and the effect of continuing such prophylaxis for new recruits entering one troop.

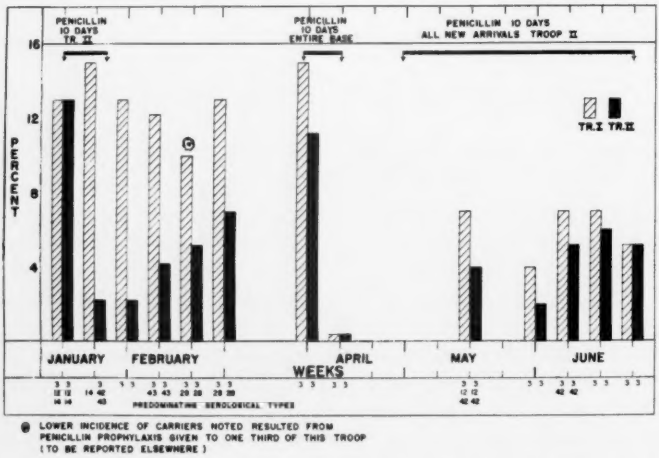

Fig. 3.—Effects of two field trials of oral penicillin prophylaxis, 250,000 units twice daily for 10 days, upon Group A Streptococcus carrier rates.

48 hours. The rate for that week was 2 per 1,000 per week, and the following week, 1.5 per 1,000 per week. In contrast, the equivalent rates for Troop I (control) were 13 per 1,000 per week and 11 per 1,000 per week. The disease rate in Troop II was maintained at a lowered level for the next five to six weeks.

B. *Oral Penicillin Administered Prophylactically to the Entire Trainee Population for Ten Days (Fig 2).*—During the third week of April, 1953, streptococcal disease rates again being elevated in both troops, the same schedule of oral penicillin administration was instituted among all personnel of the base. The effect was similar to that observed in the preceding trial, and the rate fell from 10 per 1,000 per week to less than 1 per 1,000 per week. Subsequently, each new recruit entering Troop II was treated for 10 days with the same dose of penicillin, while those entering Troop I received no treatment. Somewhat inconclusive results were noted in this latter portion of this trial, since, while the weekly streptococcal disease rates of Troop II were maintained at a lower rate than those of Troop I, statistically significant differences were not noted in all weeks.

This experiment, from which it was hoped to learn whether a streptococcally "clean" population can be maintained as such by removing these organisms from incoming members, will have to be repeated during a time when streptococcal infections are abundant.

C. *Effects of Penicillin Prophylaxis upon Group A Streptococcus Pharyngeal Carriers (Fig. 3).*—The percentage of positive cultures obtained from the throats of apparently healthy trainees were affected similarly in both mass penicillin trials. Streptococcal types demonstrated during the carrier surveys reflected the types isolated from hospitalized patients.

COMMENT

From the data presented above, crystalline buffered penicillin, administered orally in a dosage of 250,000 units twice daily for 10 days, appeared to be effective as a mass prophylactic against Group A streptococci. In other studies [2] it has been found that five days of such treatment is inadequate for this purpose. When this dosage was administered to the entire personnel of a military base, it was possible to abort a streptococcal disease epidemic, but this was done too late in the season to determine the duration of the effects of such total treatment. Since the serological types which were responsible for the hospitalized cases of streptococcal pharyngitis remained constant, it appears that the mass prophylaxis surpressed, but did not eliminate, the offending organisms.

The incidence of penicillin reactions was extremely low during both studies. During the first trial, in which Troop II received 10 days of treatment, 0.6% of the men had sensitivity reactions, while 0.7% were excused from taking the penicillin because of histories of previous penicillin reactions. Of approximately 19,000 men receiving prophylaxis during the second trial, 0.2% had mild reactions and 0.4% were excused from taking the drug. The reactions were predominately urticarial, with a few serum-sickness-like illnesses. In contrast to the experiences at Warren Air Force Base,[1] in which larger doses of penicillin had been used, there was no evidence that the orally administered penicillin produced significant amounts of diarrhea.

Although the data reported herein demonstrate that 250,000 units of penicillin orally administered twice daily will effectively control a Group A Streptococcus epidemic in a closed population, it is evident that the optimal dosage schedule still remains to be determined. Such trials are to be undertaken in the near future. It is apparent also that the findings reported herein are applicable to outbreaks in closed civilian populations as well and, further, that 250,000 units twice daily should be effective in maintaining year-round prophylaxis in patients who have had rheumatic fever. There would appear to be no purpose in continuing the practice of closing schools during streptococcal disease epidemics if the entire student body can, simultaneously, be given penicillin orally in the dose and for the period reported above.

CONCLUSIONS

Oral administration of 250,000 units of penicillin twice daily for 10 days successfully aborted a Group A Streptococcus disease epidemic and markedly reduced the carrier rate for at least five to six weeks. Few penicillin reactions were observed with this schedule.

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TREATMENT OF SUPERFICIAL THROMBOPHLEBITIS WITH PHENYLBUTAZONE (BUTAZOLIDIN)

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IN THE medical management of thrombophlebitis, reliance is placed almost completely on bed rest with elevation of the extremity, hot or cold applications, and anticoagulant therapy. Analgesics are frequently used to control pain and antibiotics to combat the chills and fever which sometimes dominate the clinical picture. The latter are of doubtful value, except in the rare case of purulent or septic phlebitis due to bacterial organisms.

These measures, when aided by the factor of time, will cause resolution of the thrombophlebitis in most instances in from one to four weeks.

There remains, however, a small but important group in whom, despite such therapy, the inflammation in the veins and adjacent tissues may remain active, resulting in considerable disability and economic loss. An agent capable of producing rapid and sustained improvement or subsidence of the phlebitis in these refractory cases would be valuable.

Phenylbutazone (Butazolidin) has been found to bring about prompt and frequently dramatic resolution of acute inflammatory conditions, including rheumatoid arthritis, gout, and peritendinitis.* It has relieved psoriatic dermatitis accompanying arthritis [3] and has recently been reported to have been effective in the treatment of erythema nodosum.[4] Because of its anti-inflammatory action in these nonspecific and unrelated conditions, phenylbutazone was tried on patients with thrombophlebitis.

METHOD

Our criteria for the selection of cases were (1) the presence of an active phlebitis, which had persisted in most instances in spite of treatment, and (2) such activity to be present primarily in the superficial veins, to obviate any difficulty in establishing the diagnosis or in studying the effect of treatment.

Of the 33 patients studied, seven were from hospital wards and outpatient clinics; the other 26 were seen in private practice at the office. With the exception of two patients, all had been on bed rest for periods of from two to six weeks, receiving the measures outlined in Table 2. These two (Cases 5 and 13) were treated after onset of phlebitis, for reasons outlined in the appended case reports.

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* References 1 and 2.

By far the commonest form of superficial phlebitis was that seen in the patient with varicosities resulting from incompetency of the saphenous systems of veins. Quite frequently their entire length could be outlined by the inflamed vein segments. Some of these patients had already had vein ligations; a few had even had vein stripping. Most had employed or were employing elastic stockings, although they stated that these seemed more of an irritant than a comfort.

As our experience grew, we included patients with an underlying systemic disease which may be considered to be related to phlebitis, i. e., two patients with thromboangiitis obliterans and a third in whom this diagnosis was suspected. Four patients had carcinoma of visceral organs.

Phenylbutazone was used in the dosage we had previously employed in the treatment of various acute rheumatic conditions: 200 mg. three times a day for three days and then 200 mg. twice a day. It was decided to discontinue the drug if there was no definite improvement within 48 hours. This represents the same time interval as occurs between use of phenylbutazone and demonstrable effect in an acutely inflamed joint. One additional stipulation was to limit its use to short courses of treatment, with repeated blood cell counts, to lessen the possibility of complications and side-effects, reports of which are recently very much in evidence.†

All patients except those hospitalized were permitted to be up and about. There was no restriction of salt or water or an attempt to use special diets.

RESULTS

The results of administration of phenylbutazone to 33 patients with superficial phlebitis are presented in Table 1.

TABLE 1.—*Results of Treatment with Phenylbutazone in Thirty-Three Patients*

Type of Phlebitis	Cases, No.	Result	
		Complete Resolution	Partial Resolution
Inflamed varicosities	22	21	1
Superficial phlebitis without varicosities	3	2	1
Migratory thrombophlebitis	1	..	1
Thromboangiitis obliterans	3*	3	..
Superficial phlebitis associated with malignant disease	4	3	1

* Although counted as one case, Patient W. F. was treated successfully on two separate occasions.

Some of the details pertinent to the individual cases are outlined in Table 2.

Typical of the course followed before and after treatment are the following representative case reports:

I. Superficial Phlebitis in Varicose Veins

CASE 1.—F. T., a woman aged 52, had acute inflammation of the lesser saphenous system in the left leg, of six weeks' duration. The entire vein could be felt as an indurated and tender cord and could easily be outlined in the skin by the discoloration and heat of the overlying tissues. There had been a poor response to bed rest with elevation, warm magnesium sulfate (Epsom salt) soaks, and antibiotics during this six-week period. In contrast, there was complete subsidence of the phlebitis within 48 hours of the use of phenylbutazone.

CASE 5.—R. K., a man aged 52, had acute phlebitis of most of the incompetent greater saphenous system in the left leg. There was moderate redness of superficial veins, with pain and swelling. The patient was treated for three days with bed rest, wet dressings, and analgesics, without change. Because of the pain and prominent constitutional symptoms, it was decided to start the patient on phenylbutazone rather than wait for possible delayed effect from the treatment just mentioned. With phenylbutazone therapy, there was rapid disappearance of pain and

† References 5-11.

TABLE 2.—*Data on Treated Patients*

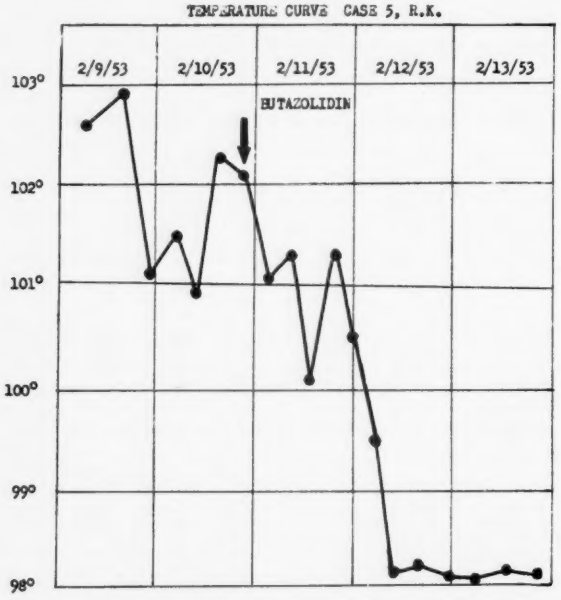
Patient	Case No.	Sex	Age, Yr.	Vein Involved	Duration of Phlebitis	Previous Treatment*	Result with Phenylbutazone		Total Dose, Gm.	Remarks
							Degree†	Hr.		
Varicose veins										
F. T.	1	F	52	Calf	6 wk.	B, E, WS, P	4+	48	3.4	See case report; no recurrence
B. S.	2	F	54	Calf	3 wk.	B, E, WS, P	4+	48	3.4	No recurrence
J. C.	3	F	46	Calf	3 wk.	B, E, WS, AN	2+	48		
							4+	96	3.0	No recurrence
R. R.	4	F	68	Calf	5 wk.	B, E, WS, AN	2+	24		
							4+	96	3.0	No recurrence
R. K.	5	M	52	Calf and thigh	3 days	B, E, WS, AN	2+	24		
							4+	48	3.4	See case report; no recurrence
N. K.	6	M	50	Calf and thigh	10 days	B, E, WS	4+	48	3.4	No recurrence
E. B.	7	F	27	Calf and thigh	5 wk.	B, E, WS, AN	4+	48	3.4	Now 5 mo. pregnant without flare-up
M. J.	8	F	63	Calf	2 wk.	B, E, WS	4+	48	3.4	No recurrence
B. B.	9	F	39	Calf and thigh	10 mo.	B, E, WS, P	4+	48	3.4	No recurrence
F. F.	10	F	45	Calf and thigh	2 mo.	B, E, WS	4+	72	7.0	No recurrence
J. S.	11	M	49	Calf and thigh	6 wk.	B, E, WS	2+	48	3.4	Returned to work outside state and not followed up
H. R.	12	M	69	Calf	1 mo.	B, E, WS	2+	48		
							4+	96	2.0	No recurrence
M. M.	13	F	31	Both thighs	7 days	B, E, WS, CC, P	4+	72	3.4	See case report; no recurrence
M. L.	14	F	62	Calf	10 days	B, E, WS	4+	72	3.4	Coexistent arteriosclerosis obliterans
K. J.	15	F	69	Calf and thigh	2 mo.	B, E, WS, P	4+	96	3.4	No recurrence
L. S.	16	M	64	Calf and thigh	9 days	B, E, CC, P	3+	48		
							4+	72	3.4	No recurrence
E. K.	17	F	62	Calf	5 wk.	B, E, WS, P, AN	2+	48		
							4+	96	5.2	No recurrence
F. K.	18	F	50	Calves	2 wk.	B, E, WS, AN	4+	48	3.4	No recurrence
S. R.	19	F	55	Calf	6 wk.	B, E, CC, WS, P	3+	72		Coexistent osteoarthritis of knees
							4+	96	5.2	also improved
A. B.	20	F	62	Calf	1 day	B, E	3+	24		
							4+	48	2.4	No recurrence
R. L.	21	F	34	Calf	5 wk.	B, E, WS, P, AN	3+	48		Recurrence in opposite thigh and calf
							4+	72	4.2	3 wk. later also successfully treated
A. P.	22	F	35	Calves	7 mo.	B, E, CC, WS, P	2+	24		
							4+	48	3.0	No recurrence
Superficial phlebitis without varicosities										
R. L.	23	F	23	Calves	12 mo.	B, E, WS, P, AN	4+	48	5.0	No recurrence
A. R.	24	M	56	Forearm	8 wk.	B, E, WS, AN	4+	72	3.4	Followed an intravenous injection
H. H.	25	F	58	Both calves	1 year	B, E, WS, P, ANTI	2+	48		
							4+	96	7.0	See case report
Thromboangiitis obliterans										
H. M.	26	M	36	Foot	2 wk.	B, E, P, AUR, STREP	4+	48	3.0	See case report; no recurrence
W. F.	27	M	49	Foot	1 wk.	B, E, TYPH, S	4+	72	3.4	See case report; one recurrence
G. D.	28	M	47	Foot and leg	2 mo.	B, E, S	See remarks		3.0	Rapid clearing of redness and swelling within 1 wk.
Migratory phlebitis										
B. E.	29	F	45	Both calves and thighs	4 years	B, E, WS, AN	2+	48		
							3+	72	15.0	See case report
Superficial phlebitis associated with malignant disease										
C. L.	30	F	37	Forearm	1 wk.	B, E, WS, AN	4+	48	3.4	See case report; comparison of therapy with and without phenylbutazone
E. McH.	31	M	61	Calf and thigh	1 mo.	B, E, WS, AN	4+	48	3.4	Postoperative cancer of stomach; no recurrence
J. W.	32	M	54	Both calves and thighs	2 wk.	B, E, AN	4+	48	3.4	Postoperative cancer of pancreas; died of basic disease
P. W.	33	M	44	All extremities	1 mo.	B, E, P, AN, ANTI	3+	48	6.8	See case report

* Abbreviations are as follows: B, bed rest; E, elevation; WS, warm soaks; CC, cold compresses; P, penicillin; AN, analgesics; AUR, chlortetracycline (Aureomycin); ANTI, anticoagulants; TYPH, typhoid vaccine; S, sympathectomy; STREP, streptomycin.

† 1+, slight improvement; 2+, moderate improvement; 3+, marked improvement; 4+, complete improvement.

inflammation within 24 hours and almost complete recovery in 48 hours. Administration of the drug was stopped after a total dosage of 3.4 gm. had been used in one week, without flare-up or recurrence. The course of the phlebitis and use of the drug are illustrated in the Chart.

CASE 13.‡—M. M., a woman aged 31, was elected for early treatment with phenylbutazone because she was six months' pregnant and had developed an acute phlebitis of segments of the internal saphenous system, first in one thigh and then in the other. She had been kept in bed for one week by her physician but had had no improvement, despite cold packs, warm magnesium sulfate soaks, and penicillin. Rather, it seemed that each day saw further spread of the phlebitis. Because of her pregnancy, this progression was viewed with great concern, not only by the patient and her husband but by her doctor, who thought that vein ligation would be necessary.



Temperature curve of Patient R. K. (Case 5).

One of us (IDS), on being called in to see her, thought that phenylbutazone might be tried first. The response was very gratifying in that pain rapidly disappeared, within 24 hours, and the redness and swelling had disappeared by 72 hours. Some induration of the thrombosed vein persisted, but without signs of activity.

II. Superficial Phlebitis Without Varicosities

CASE 25.—In H. H., a woman aged 58, both great saphenous systems had been the seat of a phlebitis for one year. Hard tender indurated vein segments were felt on the inner aspect of both legs for almost their entire length. There was considerable interference in walking because of pain. The patient was in a disturbed emotional state because of the duration of her disease and because anticoagulants and other measures had been of no avail. With phenylbutazone there was softening of the periphlebitic indurated areas and striking relief from pain. The patient became ambulant four days after the start of treatment. Phenylbutazone in doses of 100 mg. daily was continued because of the tendency to recurrence when drug was stopped.

‡M. M. has since delivered a premature infant. Her legs have been completely asymptomatic from the first week of treatment.

III. Thromboangiitis Obliterans

CASE 26.—H. M., a man aged 36, had recurrent bouts of superficial phlebitis in the lower extremities of 11 years' duration. A vein ligation had been done six years before, without effect on the phlebitis. Although there was no clinical arterial impairment, thromboangiitis obliterans was suspected. The patient had been in the hospital six months for the present attack. The dorsal veins of the right foot and ankle were diffusely inflamed, red, and tender. Forty-eight hours after use of phenylbutazone there was complete subsidence of the phlebitis. This has been maintained. Total dosage used was 5.0 gm.

CASE 27.—W. F., a man aged 49, has had established Buerger's disease of many years' duration, with recurrent flare-ups of superficial phlebitis. At present there is involvement of the dorsal veins of the left foot and the mesial aspect of the leg, where the vessels were inflamed and indurated. Within 72 hours after use of phenylbutazone there was complete subsidence of phlebitis, which has been maintained.§ Prior to this time, there had been continuous vein activity unchecked by fever therapy (typhoid vaccine) and sympathectomy as well as other measures.

IV. Migratory Superficial Thrombophlebitis

CASE 29.—B. E., a woman aged 45 has had migrating thrombophlebitis in the superficial veins of both lower extremities for the past four years, with no relief from any types of treatment. Many small varicosities are present; there is no arterial disease. This patient, like the previous one, had complete subsidence of her phlebitis with phenylbutazone therapy. Here too, this seems to be chiefly suppressive therapy; consequently, a maintenance dose of 100 mg. twice daily is being continued. There has been no vein activity for over six months.

V. Superficial Phlebitis Associated with Malignant Disease

CASE 30.—C. L., a woman aged 37, has rheumatic cardiac disease, with radical mastectomy for adenocarcinoma performed one and one-half years previously. One year ago there was acute phlebitis of the superficial vein over the anterior surface of the left elbow, which subsided after several weeks of treatment with rest, heat, and antibiotics. Six months later there was a flare-up in the superficial veins of the left upper arm. This time there was complete subsidence with phenylbutazone therapy within 48 hours. No recurrence has been found on follow-up. Total dosage was 3.4 gm. In this patient there was no evidence of metastatic disease.

CASE 33.—P. W., a man aged 44, had postoperative bronchogenic carcinoma with metastases. There was involvement of all superficial and some deep veins in all extremities. The veins were hard and tender and felt like cords; there was relatively little surrounding inflammation. There was no response to antibiotics, vasodilators, and anticoagulants. Marked diminution of pain and some softening of infiltrated veins occurred with phenylbutazone therapy. When the drug was discontinued, there was recurrence of original symptoms. Again the condition responded to use of phenylbutazone, and the patient has been kept almost symptom-free on a maintenance dose of 200 mg. twice daily.

COMMENT

The improvement manifest in our 33 || patients with acute superficial thrombophlebitis treated with phenylbutazone was uniform and striking. No previous method of therapy for this condition in our experience with this disorder, in both hospitalized and office patients, has produced as rapid or satisfactory an effect. The morbidity and disability from recurrent or continuous vein inflammation was in some instances reduced from a prolonged period to 48 and 72 hours with administration of phenylbutazone. In some cases, which were also successfully treated, the existence of phlebitic activity had been present for long periods, months to years. The

§ Approximately three months after this episode, another acute phlebitic flare-up was noted in the same foot. The patient requested the same drug (phenylbutazone) which had given him such marked relief in such a short time. The response this time was equally good.

|| Seventeen additional patients have been treated successfully since this article was submitted for publication.

effect of the drug was particularly impressive in that improvement in most cases followed an adequate trial of but unsatisfactory response to other types of treatment which are usually effective.

In the nonhospitalized patients all previous therapy was abandoned and the drug was given with the patient ambulant and without special instructions other than to report immediately any untoward manifestations denoting drug sensitivity. Blood cell counts were done only for those patients to whom the drug was administered past the stated trial period of one week (seven instances). No allergic reactions were observed. However, in Case 20 it was felt that the attack of renal colic might be attributed to the drug.

In Cases 10, 24, and 28, although remission was prompt and complete, there was a tendency for recurrence; consequently, in comparison to the other patients, large doses were used as suppressive treatment. These were discontinued after totals of 7, 7, and 15 gm., respectively, had been taken. No further recurrence was then noted.

The mode of action of phenylbutazone is not yet completely understood. It has an analgesic action which is of a high order and is probably very helpful in reducing the pain associated with thrombophlebitis. We were more interested in its other behavior, preventing or depressing inflammation, which is often so dramatic in the acutely inflamed joint of gout or of rheumatoid arthritis. Experimental evidence for this action is also convincing, i. e., it will delay or inhibit the erythema produced by exposure to ultraviolet light; it will delay or inhibit the edema which normally follows injection of certain irritants.¶

In the management of thrombophlebitis we have found this combination of analgesic and anti-inflammatory actions to be almost uniformly beneficial; the pain, swelling, much of the induration, and all the redness of the superficial veins and adjacent tissues seem to melt away within 24 hours in some few instances and to disappear by 72 to 96 hours in most cases.

Of particular interest is the response in the two proved cases and one probable case of thromboangiitis obliterans. To our knowledge this is the first time that such a specific phlebitis has been influenced favorably by medication. Our experience with cortisone in several instances of Buerger's disease has not indicated any definite effect. Since thromboangiitis obliterans is a panvasculitis, involving not only venous channels but also the arterial tree, the effect on the latter is something that merits further study.

The dangers from the use of phenylbutazone are real and frequently reported and must be stressed.# The drug has been shown to have toxic effects on the bone marrow, with production of granulocytopenia, anemia, or both. Frequent blood cell counts, daily if possible, should be made, and use of the drug should be stopped if there is any sharp change in either the red or white cell count or if fever and sore throat occur.

Because of the tendency to gastrointestinal irritation and even hemorrhage, the drug is best given with or shortly after meals and the patient is cautioned to watch the color of his stools and to halt use of the drug if vomiting or bleeding takes place.

Skin eruptions are not too uncommon. They are usually morbilliform in nature and tend to disappear on withdrawal of the drug. However, there have been instances

¶ References 12 and 13.

References 5-11.

of severe dermatitis, some resulting in death, due to exfoliation of skin. The patient should be made aware of this possibility and advised to report any skin manifestation immediately.

Phenylbutazone is therefore a drug to be used with caution and respect under any circumstance. Under competent and constant supervision, particularly with short and limited periods of treatment, we believe that this drug can be used with relative safety and may have an important place in the treatment of thrombophlebitis. We have not encountered any of the complications enumerated above in any of our treated patients.

SUMMARY AND CONCLUSIONS

Thirty-three patients with superficial thrombophlebitis due to various causes, many not responding to other forms of therapy, were treated with phenylbutazone (Butazolidin). They were ambulant and not restricted in salt, fluids, or diet. The drug was used for one week in the majority of cases in daily dosage of 300 to 600 mg. for a total dose of 3.0 to 3.5 gm.

In all patients there was rapid complete or partial regression of the vein inflammation.

Phenylbutazone reduces the duration of bed rest, disability, and economic loss. As such, it is a useful adjunct in the treatment of thrombophlebitis.

Because of the possibility of toxic effects on the bone marrow, gastrointestinal tract, skin, and other organs, every effort should be made to safeguard the patient by frequent examinations and blood cell counts.

Additional clinical and physiological studies are being undertaken to determine the possible mode of action of phenylbutazone in various vascular disorders.

Dr. Joseph Cole, Mt. Vernon, N. Y., provided data on Cases 4 and 12; Dr. William J. Van Wie, Mt. Vernon, N. Y., provided data on Case 29, and Dr. Karl Harpuder, New York, provided data on Case 28.

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SEROLOGIC STUDIES ON OUTBREAK OF PULMONARY DISEASE AT CAMP GRUBER, OKLA.

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AN OUTBREAK of an unusual form of pulmonary disease occurred at Camp Gruber, Okla., in March, 1944.* The illness affected 27 men and was characterized by sudden onset and severe and prolonged clinical course with slow recovery. Most patients showed diffuse infiltration of the lungs. The etiology of the disease was not known. All the men involved had spent some time 10 days previously in a storm cellar on the military reservation.

In 1952, Histoplasma capsulatum was isolated from the soil in the storm cellar.[3] In 1951 and 1952, skin tests were performed on 22 of the men who were involved in the pneumonitis outbreak; all reacted to histoplasmin, whereas only 6 reacted to tuberculin, 3 to blastomycin, and 1 to coccidioidin.[3] Disseminated pulmonary calcification was observed by x-ray examination in 16 of 22 men who had pneumonitis at Camp Gruber. On the contrary, such calcifications could not be found in eight men who were in the same army organization as the men in the outbreak but who did not develop pulmonary disease.[3]

During the period of acute illness and for months thereafter, blood was drawn many times for serologic assay. However, most of these serum samples were used for other studies prior to the time the tests about to be described were conducted. The remaining sera, which were collected in April, May, and June, 1944, were obtained through the courtesy and cooperation of Dr. John H. Dingle and the Commission on Acute Respiratory Diseases, of the Armed Forces Epidemiological Board. In addition, sera collected in 1951 and 1952 were obtained from 22 of the patients in the pneumonitis outbreaks. It is regretted that complete sets of sera were not available, since the serologic status of the patients at comparable stages of illness could not be determined. However, it will be shown in this paper that at least one of the sera from each of the patients involved in the epidemic had antibodies against H. capsulatum.

METHOD

All sera were tested for antibodies against H. capsulatum by both precipitation [4] and complement-fixation techniques.[5] In the precipitation tests, equal quantities of antiserum and dilutions of antigen were drawn into 3 in. (7.5 cm.) lengths of capillary tubing, incubated for two hours

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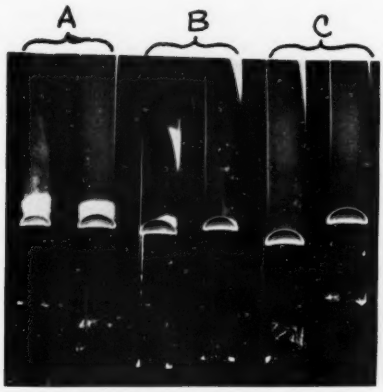
* References 1 and 2.

at 37 C., and refrigerated for 36 hours at 3 to 5 C. before reading. The precipitating antigen was the filtrate from the growth of the mycelium of isolate No. 6510 in an asparagine-glucose medium [6] incubated for 60 to 90 days at room temperature (100 ml. of medium per 250 ml. flask). The presence of a precipitate was considered as an indication of antibody to H. capsulatum, with the exception of very slight precipitates in antigen dilutions of 1:2 and 1:4, which were considered "doubtful" (Fig.).

In the complement-fixation tests, whole cells of the yeastlike phase of isolate No. 6515 were used as antigen. These had been grown in a "casamino acid" medium under constant rotation at 37 C. for four to five days,[7] killed by heating at 56 C. for one hour, washed in saline solution, and stored in 1:10,000 thimerosal, N. F. (Merthiolate) solution at 3 to 5 C. A Bengtson-type test was employed,[8] with 2 units of hemolysin, 2 units of complement, and that amount of antigen that gave the highest complement-fixation titer with a serum of known capacity. Sera with titers of 1:8 or higher were considered to indicate the presence of antibodies against H. capsulatum, while titers of 1:2 and 1:4 were classified as doubtfully indicating antibodies.

Sera from four groups were tested as follows: Group A contained 27 patients who had been in the storm cellar in March, 1944, and who had been involved in the outbreak; group C included 9 patients whose sera were obtained in early 1944 and who were members of the same



Precipitation tests with undiluted human sera and 1:5 and 1:10 dilutions of antigen. *A*, "positive" serum; *B*, "doubtful" serum; *C*, "negative" serum. Positive sera usually continued to form heavy precipitates when the antigen was diluted as much as several hundredfold. Doubtful sera showed slight precipitates, which frequently no longer formed when the antigen was diluted as little as tenfold. No evidence of inhibition attributable to antibody excess was obtained, since dilution of doubtful or negative sera did not enhance precipitation.

army organization but who remained well; Group D consisted of 8 patients on wards in Camp Gruber from whom control sputum specimens were obtained; Group X was composed of 6 civilians who lived near or were employed at Camp Gruber.

With the exception of the follow-up sera obtained in 1951 and 1952, the only samples available were those collected during April, May, or June, 1944, and varied in number from one to five per person. Only five persons had serum samples from a coinciding date. The serological tests were performed in a manner which made it impossible for the operators to know to which group each individual serum belonged.

RESULTS

Of the 27 patients with pulmonary disease, 25 had diagnostic levels of precipitins and/or complement-fixing antibodies (Table 1) in one or more of the serum samples. Two had precipitins and complement-fixing antibodies of doubtful diagnostic titers. None of the 27 showed complete absence of both types of antibodies. On the con-

trary, sera of persons in control Groups C, D, and X were negative, with the exception of three whose sera showed precipitins to a titer of 1:2 (Table 1) and of one (in Group X) who had precipitins at a diagnostic level. The latter, however, was known to have entered the cellar on May 17, 1944, and to have become ill on May 25, 1944. Two serum samples were obtained from this patient on June 5 and June 20 of the same year. The initial serum had no demonstrable antibodies, but the second did have precipitins of diagnostic titer. Complement-fixation and precipitation tests showed no detectable antibodies in sera obtained from this patient in 1953, although the skin test with histoplasmin was positive. Chest x-ray showed a miliary calcification which resembled those seen in the patients in Group A.

If titers of 1:4 and above had been considered "positive" and titers of 1:2 and below "negative," then all 27 of the sera from the pneumonitis-outbreak patients would be considered "positive" and all of the sera in control Groups C and D would be "negative."

When the individual titers of the pneumonitis patients were examined, 22 of 27 showed peak complement-fixing antibodies in titers of 1:8 or above (Table 2), and 2, in titers of 1:2 to 1:4; 3 had no complement-fixing antibodies at a titer of 1:2

TABLE 1.—*Summary of Serologic Activity of Sera from Pneumonitis Patients, as Well as from Control Groups*

	Sera No.		
	Positive	Doubtful	Negative
Group A	25	2	0
Group C	0	1	8
Group D	0	2	6
Group X	1	0	5

during the period tested. Twenty-four of the 27 had precipitins at some time during April, May, or June. It is possible that the other three may have had precipitins but that the sera were not collected during the period precipitins were present.

Of the eight patients from whom sera were still available for the months of April, May, and June, four had their peak titer in April, three in May, and one in June. Of those 11 patients from whom sera were available for only two months, four had the peak titers in April, seven in May, and none in June. Of the peak titers of 1:64 and higher, four occurred in April, three in May, and none in June. It would, therefore, seem that the titers were on the decline in June and, to a lesser extent, also in May.

Of 22 patients with pulmonary disease who were bled in 1951 or 1952, seven to eight years after the epidemic, 2 had sera with complement-fixing titers of 1:8 or higher; 10 had sera with titers from 1:2 to 1:4, and 9 had sera with no detectable antibodies. Of the nine sera from control Groups C and D, none had detectable complement-fixing antibodies against H. capsulatum.

The sera were also tested by both complement-fixation and precipitation techniques against antigens from Blastomyces dermatitidis and Coccidioides immitis. The whole cell of the yeast phase of B. dermatitidis was used as the complement-fixing antigen, and blastomycin was used as the precipitating antigen. Coccidioidin † was

† Obtained through the courtesy of Dr. C. E. Smith, School of Public Health, University of California, Berkeley, Calif.

used as the antigen in both types of serologic tests for coccidioidomycosis. Of the 22 in Group A who had complement-fixing antibodies against H. capsulatum, only two had antibodies against B. dermatitidis and two others had antibodies against C. immitis. These four sera had heterologous titers against the heterologous antigens markedly lower than those obtained with H. capsulatum. A greater number of cross reactions were observed in the precipitin test with antigens from B. dermatitidis and C. immitis. Of the 24 patients whose sera had precipitins against H. capsulatum, 9 had antibodies against B. dermatitidis. Two of these nine also had precipitins against C. immitis. In addition, the person in Group X who had precipitins against

TABLE 2.—*Peak Titers on Sera from 27 Patients Who Had Pulmonary Disease*

Patients	Complement-Fixation Test *		Precipitation Test *	
	1944	1951-1952	1944	1951-1952
C. B.	8	16	+	d
W. B.	0	x	d	x
J. B.	8	0	d	—
L. B.	2	2	d	—
R. C.	16	4	d	—
J. D.	16	2	d	—
L. D.	16	x	+	x
C. F.	32	4	d	—
J. H.	0	0	+	d
J. H.	16	AC	d	—
D. J.	8	0	d	—
E. M.	8	2	d	—
A. M.	8	0	—	—
R. N.	0	0	+	—
R. N.	32	x	+	x
W. P.	16	0	d	—
J. P.	16	2	—	—
L. P.	16	2	d	—
G. P.	8	x	d	x
J. P.	64	4	—	—
I. R.	16	x	d	x
H. R.	32	4	+	—
H. R.	8	x	d	x
H. S.	4	0	+	—
T. S.	16	4	+	—
T. W.	32	0	+	—
R. W.	8	8	+	+

* AC, anticomplementary sera; +, heavy precipitates; d, slight or doubtful precipitates; —, indicates no precipitates; x, indicates no serum available.

H. capsulatum also had precipitins against the other two fungus antigens. None of the other persons in control Groups C, D, and X showed antibodies against B. dermatitidis or C. immitis.

COMMENT AND SUMMARY

Serologic results by both complement-fixation and precipitation techniques indicate that Histoplasma capsulatum was the etiologic agent in the pneumonitis outbreak that occurred in 27 men after their entrance into an abandoned storm cellar at Camp Gruber, Okla. This conclusion is based on the following facts. A. Antibodies against H. capsulatum were present in the sera from each of the men involved in the pneumonitis outbreak. The sera tested had been collected during April, May, or June following the exposure in the cellar. B. The control sera, from persons who

had not been in the cellar, did not have complement-fixing antibodies against H. capsulatum. Only 3 of 19 had slight precipitates at an antigen dilution of 1:2. The person in the civilian group who developed marked precipitins against H. capsulatum subsequently had entered the storm cellar and had become ill shortly before the time the serum was drawn. C. Titers were lower in June than in April, a fact which suggests that the infection occurred before April. D. Twelve of 22 sera collected from the pneumonitis patients in 1951 to 1952 showed low-titered antibodies against antigens from H. capsulatum, but not against antigens from Blastomyces dermatitidis and Coccidioides immitis. None of nine sera from the control groups had any detectable antibodies. E. Reactions of the patients' sera with antigens from B. dermatitidis and C. immitis were very slight.

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COEXISTING DIABETES MELLITUS AND ADDISON'S DISEASE

Observations and Report of a Case in a Ten-Year-Old Boy

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THE COEXISTENCE of diabetes mellitus and Addison's disease is a rarity. In a review of the literature and from personal communication, we have found reports of only 45 cases (Table 1). The earliest case, reported in 1866,[1] was thought to be one of diabetes alone until postmortem examination revealed the presence of bilateral adrenal tuberculosis. In this case, as well as in the cases reported by West,[2] Rabé,[3] Montgomery,[4] Umber,[7] and Brookfield and Corbett,[14] reasonable doubt exists as to the presence of Addison's disease in a clinical sense. Since 1926, instances of coexistence of diabetes and Addison's disease have been recognized with increasing frequency. In this paper, we report one additional patient and present further information regarding another (Case 43 in Table 1), previously described briefly by Thorn and co-workers.[42] Case 1 is believed to be the youngest patient in whom the presence of the two conditions has been recognized.

REPORT OF CASES

CASE 1.—A. C. (Case 46 in Table 1) was first seen on April 27, 1943, at the age of 2½ years. He had been well until several weeks previously, when he had developed weakness, polyphagia, polyuria, and enuresis. On the day of first observation he appeared drowsy and was taken to a hospital, where his blood sugar was found to be 247 mg. per 100 cc. Marked glycosuria and acetonuria were present. He was given 25 units of insulin and was transferred to the New England Deaconess Hospital.

A survey of the past history revealed no significant illness except pertussis. A maternal great aunt and a maternal cousin were said to have had diabetes mellitus. A brother had died at the age of 10 months of undetermined cause. A sister, 6 months old, and both parents were well.

Physical examination showed no abnormalities except for moderate drowsiness and dehydration; the liver was palpable 2 cm. below the costal margin. The patient's height was 97.8 cm. (38½ in.), and his weight, 11.8 kg. (26 lb.). The blood sugar was 104 mg. per 100 cc., rising to 253 mg. by the following morning. His course was uneventful. He was discharged from the hospital after 11 days on a regimen of 2 units of crystalline and 12 units of protamine zinc insulin in separate injections daily before breakfast and a diet of carbohydrate 144 gm., protein 64 gm., and fat 75 gm.

Interval History.—During the ensuing eight years, the patient was seen at approximate yearly intervals. He entered the New England Deaconess Hospital five times for regulation of diabetes and, in the summers of 1948, 1949, and 1950, attended the Elliott P. Joslin Camp for diabetic boys at Charlton, Mass. Close adherence to diet was rarely achieved at home and his diabetes was usually poorly controlled. Random blood sugar values obtained at office visits

From the Baker Clinic Research Laboratory, New England Deaconess Hospital, and the Joslin Clinic.

TABLE 1.—*Summary of Reported Cases in Which Diabetes Mellitus and Addison's Disease Coexisted*

Case No.	Author	Year Reported	Sex	Age at Death, Yr.	Age at Dual Diag., Yr.*	Duration, Yr.†		Insulin Dose, Units		Autopsy Findings			Remarks
						DM	AD	Before AD	After AD	Adrenals	Pancreas	Other	
1	Ogle [1]	1866	M	55	‡	6.2	?	..	..	TB	.....	Pulmonary TB	.....
2	West [2]	1890	M	49	‡	0.5	?	..	..	Fibrosis and atrophy	?	?	"Greyish, cyanotic hue to skin"
3	Rabé [3]	1900	M	49	‡	3?	?	..	..	Enlargement; TB	Fibrosis; hemochromatosis	Generalized hemochromatosis, cirrhosis, pulm. TB, skin showed melanin and hemosiderin pigment	DM, AD, and hemochromatosis; questionable
4	Montgomery [4]	1912	M	45	‡	1.5	?	..	..	Atrophy; TB	Fibrosis	Lung abscess	.....
5	Unverricht [5]	1926	M	32	32	6	weeks	40	20-0	TB	?	?	.....
6	Arnett [6]	1927	F	39	37	2	3	..	50-20	Absence (rt); fibrosis (lt)	.....	.....	AD preceded DM
7	Umber [7]	1928	F	52§	52	2	0.5	0	42-8	.....	.....	.....	.....
8	.....	....	M	70§	69	8	1	..	40	.....	.....	.....	.....
9	Rowntree & Snell [8] also, Snell & Rowntree,[9] 1929	1931	M	36	35	2	1	?	20-30	Atrophy	Atrophy	Thyroid hypertrophy	Post-thyroidectomy death, insulin hypoglycemia and Addisonian crisis (?)
10	.....	....	M	?	?	6	1.5	?	?	Atrophy	Atrophy	Gastritis, proctitis, sigmoiditis	.....
11	Simpson [10] also, Crooke & Russell,[11] 1935; Simpson,[12] 1949	1932	M	16	16	0.1	1	..	15-0	Fibrosis and atrophy	Fibrosis	Nephritis, pituitary showed diminished baso. and acido.; many large chromophobes	AD preceded DM
12	Gowen [13]	1932	F	54	54	0.5	0.5	(Diet only)		Atrophy	Fibrosis and hyalinization	Increased liver glycogen	Probable simultaneous onset
13	Brookfield & Corbett [14]	1934	F	61	‡	weeks	?	(30-15 q. 3 h.)		Atrophy	Fibrosis and hyalinization	.....	.....
14	Rogoff [15]	1936	M	25	24	5	1	48-60	5	?	?	?	Bilateral adrenal denervation for relief of DM 1½ and 1 yr. before death; autopsy refused
15	Heim [16]	1940	M	29	29	8	< 1	40-80	0	Fibrosis and atrophy	Fibrosis	.....	.....
16	Rhind & Wilson [17]	1941	F	32	31	1	2	..	48-60	Fibrosis and atrophy	Fibrosis	Small chromophobe adenoma of pituitary; thyroid resembled Graves' disease	AD preceded DM
17	Bowen and others [18]	1942	F	76	?	?	?	0	0	TB	Small	TB pericarditis; pulm. TB; diabetic nephropathy	.....
18	McCullagh [19]	1942	M	"young man"§		7	1	40-120	"less"	.....	.....	.....	Also necrobiosis lipoidica diabeticorum
19	Koepf & Bowen, cited by Thorn & Clinton [44]	1943	M	20	18	2	2	(Diet only)		Atrophy	?	?	Simultaneous onset

20	Nix [20]	1943	M	39	‡	1.5	?	..	30-0	Absence; atrophy and fibrosis	?	?	
21	Bickel [21]	1945	M	36§	35	7	1	50	10				
22	Jonáš [22]	1946	F	20	20	0.3	2	..	30-14	Absence; hypoplasia	Hypoplasia		AD preceded DM
23	Devitt & Murphy [23]	1947	F	28	28	4	0.5	10-30	0-30	Fibrosis and atrophy	Fibrosis		
24	Sprague and others [24] also, Sprague,‖ 1952	1947	F	40	37	10	3	40-50	0-32	Atrophy	Fatty infiltration; no hyalinization	Bilat. tubo-ovarian abscess and pyosalpinx, pelvic peritonitis	Insulin dosage proportional to dosage of preparations for AD
25			F	31	30	2	1	20-30	20-30	?	?	?	Death due to ? hypoglycemia
26			M	59	56	12	3.5	0	0	?	?	?	Death due to widespread TB
27	Adler [25]	1947	F	20§	19	3	1	75	45				
28	Ernberg [26]	1947	M	46	45	1	4	..	40-8	Atrophy	Atrophy	Mild cirrhosis; abdominal TB; lymphadenopathy	AD preceded DM
29	Soffer [27] also, Soffer,[28] 1951	1948	M	42§	41	1	3	..	10				AD preceded DM
30	Lowrie and others [29]	1948	F	30§	29	1	3	..	12				AD preceded DM
31	Bernstein [30] also, Armstrong,[31] 1944; Bloomfield,[32] 1939	1948	M	39	31	9	8	56	2-0	Absence; hypoplasia	Small	Fibrosis of thyroid and pituitary	Clinically resembled progressive hypothyroidism
32	Doetsch [33]	1948	F	57	55	4	2	45	35-20	Atrophy	Fibrosis and atrophy	Melanin skin pigmentation	DM more severe with start of AD
33	Knowlton & Kritzler [34]	1949	F	26	24	2	7	..	4-12	Small, fibrous remnants	Small	Pituitary degeneration with diminished chromophobes	AD preceded DM
34	Crampton and others [35]	1949	F	60	59	20	1	20-30	8	TB	Fibrosis	Chronic glomerulonephritis	
35	Simpson [12] also, Simpson,[36] 1950	1949	M	37	32	26	5	72	24-6	Absence; atrophy	Atrophy		Infantilism
36			M	20§	19	1	1.5	..	32-14				AD preceded DM
37	Sprague and others [37] also, Sprague,‖ 1952	1949	F	36§	31	16	5	50-75	7-56				
38	van Buchem [38]	1950	M	48	48	0.7	3	..	8-0	Fibrosis	?	Serous pericarditis; old pulm. TB	AD preceded DM
39	Ward and others [39] also, Levy,[40] 1952; Sprague,‖ 1952	1950	M	44§	41	16	3	56-60	34				
40	Kaiser [41]	1950	F	61§	57	10	4	30-40	0-20				
41	Adler, cited by Soffer [28]	1951	F	25§	?	?	?	55	5				
42	Thorn and others [42]	1951	M	35§	27	8	13	..	8-16				AD preceded DM
43	Also, Thorn and others,[42] 1949; Thorn & Clinton,[44] 1943		F	42§	40	17	2	40	20-36				
44	Sprague ‖	1952	M	53§	41	12	12	0	0				Simultaneous onset
45			F	54§	53	7	1	26	25-60				Myxedema recently developed
46	Present report	1953	M	12§	10	9.5	2	14-44	12-28				

* Dual Diag., earliest recognition of coexistence of the two conditions.
† At death or at last report. DM, diabetes mellitus; AD, Addison's disease.
‡ Diagnosis not made during life.
§ Subject living at time of original report.
‖ Personal communication to the authors.

ranged from 31 to 410 mg. per 100 cc. On June 27, 1949, he was admitted to the hospital in acidosis with a blood sugar of 347 mg. per 100 cc. and a plasma CO_2 content of 9 mEq. per liter. Recovery took place after appropriate treatment with insulin and fluids.

In spite of unsatisfactory diabetic control, the patient remained in good general health; growth and development were normal. When he reported at camp in July, 1949, his height was 127 cm. (50 in.) and his weight was 25.7 kg. (56½ lb.). His insulin requirement had increased gradually over the years to 44 units of isophane (NPH) insulin daily, and his diet had been increased to carbohydrate 204 gm., protein 102 gm., and fat 101 gm.

During the first few months of 1950 the patient developed anorexia and had frequent gastrointestinal upsets. When he was seen at an office visit in March, 1950, his blood sugar two and three-quarters hours after a meal was 394 mg. per 100 cc., although he was still taking 44 units of isophane insulin daily. By the time he returned to camp, in July, his insulin requirement had dropped to 24 units; he reported having had frequent insulin reactions at home after supper and occasional early morning convulsions. He had apparently recovered from his gastrointestinal disorder. His height was now 130 cm. (51¼ in.), and his weight was 27.5 kg. (60½ lb.). His stay at camp was not remarkable except for dietary indiscretions and occasional insulin reactions. He took part in athletics as usual.

On June 9, 1951, the patient was again admitted to the New England Deaconess Hospital. He had continued to take 24 units of isophane insulin daily. He had had convulsions twice recently. Four days before admission he developed nausea, vomiting, and diarrhea and was able to take nothing by mouth. The daily dose of insulin was reduced to 12 units. Two days before admission, he became unconscious and was taken to another hospital, where blood sugar values on successive days were reported to be 30 mg., 23 mg., and 325 mg. per 100 cc., respectively. He was then transferred to the New England Deaconess Hospital. On admission, the patient was drowsy, barely responding to questions. The skin was cold, and there was a mottled reddish-blue discoloration of the fingernail beds and feet. A few black freckles were noted on the back, and there was a questionable increase in pigmentation in the creases of the left elbow, but the skin and mucous membranes were otherwise normally pigmented. His height was 134.4 cm. (52½ in.) and he weighed 25.9 kg. (57 lb.). The blood pressure was 70/40 mm. Hg; the pulse rate was 112 and was regular. He appeared well hydrated. The tonsils were moderately large but did not appear infected, and there was no lymphadenopathy. The heart, lungs, and abdomen were normal. The patellar reflexes were not obtained.

Studies on admission revealed a blood sugar of 142 mg. per 100 cc., CO_2 content of 14 mEq. per liter, nonprotein nitrogen of 30 mg. per 100 cc., and hemoglobin 15.3 gm. per 100 cc. The white cell count was 11,450, with a normal differential count. Urinalysis showed 2.4% sugar and no diacetic acid or albumin, and the sediment contained 30 to 40 white blood cells and 10 to 15 red blood corpuscles per high-power field. (The patient had been catheterized prior to admission.) An electrocardiogram taken with three standard leads showed no abnormality except for sinus tachycardia.

It was believed that the patient's condition was a manifestation of posthypoglycemic stupor and electrolyte depletion. He was given solutions of glucose and sodium chloride parenterally and isophane insulin was administered in amounts varying from 12 to 24 units per day.

On June 10 the patient was still semistuporous. He was given 25 cc. of aqueous adrenal cortex extract intramuscularly, with equivocal results. On June 11 his extremities were warmer and the blood pressure was 90/50. A four-lead electrocardiogram again showed no abnormality. On June 12 he was more alert and began to eat small amounts of food for the first time. The serum sodium was 115 mEq., rising to 129 mEq. per liter following the administration of 200 cc. of 5% solution of sodium chloride intravenously. The patellar reflexes were now brisk. The patient's course was complicated by the development of cellulitis of both thighs (at the sites of hypodermoclyses), which responded slowly to treatment, which included the administration of streptomycin and penicillin procaine. A rash appeared over the back but promptly cleared when sulfisoxazole (Gantrisin) was substituted for the antibiotics. The urine sediment became normal, and a urine culture showed no growth.

By June 20 the patient appeared much improved, but he continued to have frequent episodes of vomiting. He failed to regain his usual strength and sense of well-being. Studies of his adrenal status were then pursued more intensely (Tables 1 and 2), and the diagnosis of primary adrenal insufficiency was established.

Specific therapy was begun, on June 30, with the daily intramuscular injection of desoxycorticosterone acetate (DOCA); a dose of 2.5 mg. was given for two days, and then 3.5 mg. was given daily. Sodium chloride, 0.5 gm., was given daily by mouth. At the end of a week, slight periorbital and ankle edema had developed and the patient had gained 1.6 kg. (3½ lb.). He was still listless and anorexic. The serum sodium had risen to 139 mEq. per liter, and the serum potassium, which had persistently been slightly elevated, was now 4.5 mEq. per liter. Supplementary sodium chloride was discontinued, and desoxycorticosterone acetate was given in 2.0 mg. doses until July 14, when a single 60 mg. injection of desoxycorticosterone phenylacetate (Ciba) was administered. Cortisone was begun in dosage of 12.5 mg. orally every 12 hours. On July 24 the patient appeared and acted quite well. His insulin requirement had increased to 44 units of isophane insulin. On July 28 he was discharged to the Elliott P. Joslin Camp, where he took part normally in the usual camp activities, including competitive athletics. The cortisone was reduced to 6.25 mg. twice daily, and the insulin dosage was established at 28 units daily.

TABLE 2.—*Results of Determinations of Constituents of Blood Plasma in Case 1 (A. C.; Case 46 in Table 1)*

Date	Sodium, mEq./Liter	Potassium, mEq./Liter	Chloride, mEq./Liter	CO_2 Content, mEq./Liter	Remarks
1951					
6/12	115	6.0	88	18	.....
6/14	129	...	..	..	200 cc. 5% NaCl given I. V. 6/13
6/20	127	5.8	..	..	.....
6/26	125	6.2	..	..	.....
6/30	115	6.7	..	..	Desoxycorticosterone acetate started
7/ 8	139	4.5	..	..	I. M. administration of long-acting desoxycorticosterone acetate began on 7/14 *
1952					
4/ 2	126	4.0	98	..	.....
1953					
9/ 4	138	5.9	92	..	.....

* Desoxycorticosterone phenylacetate was given in dosage of 60 mg. at intervals of about six weeks until February, 1952, when desoxycorticosterone trimethylacetate was begun, in dosage of 60 mg. monthly. During entire period, 12.5 to 18.75 mg. cortisone were given by mouth daily.

Special Studies.—The results of special studies are shown in Tables 2 and 3. It will be noted that, in spite of the administration of physiologic and hypertonic saline solution, the serum sodium remained well below normal until desoxycorticosterone acetate therapy was begun. Serum potassium levels tended to be slightly high until desoxycorticosterone acetate was administered.

The results of a series of eosinophile tests carried out as described by Renold and co-workers [45] and the results of a number of 24-hour urine collections for 17-ketosteroid determinations are listed in Table 2. The eosinophile count failed to fall after the subcutaneous injection of epinephrine and intramuscular injection of corticotropin (ACTH). Four intravenous corticotropin tests failed to produce a significant decrease. The 17-ketosteroid excretion was extremely low (normal for this age is 2.6 mg. per 24 hours) [46] and was not increased by the repeated intravenous administration of corticotropin.

The Robinson-Kepler-Power water test was positive. The night urine volume was 362 cc., while the largest hourly day volume was only 70 cc. The calculated "A" value was 8 (positive if "A" is less than 25).

Roentgenograms of the skull showed a normal pituitary fossa. The chest film was also normal. Films of the hands and wrists indicated a bone age of 10 years (chronological age was 10½ years). The uptake of radioactive iodine following the giving of 25 μc was 39% in 24

hours. The protein-bound iodine of the blood plasma was 6.1 γ per 100 cc. (normal is 3 to 7 γ per 100 cc.). There was, therefore, no evidence of pituitary or thyroid dysfunction. An electroencephalogram showed a mildly slowed response.

Subsequent Course.—From the summer of 1951 until the present (December, 1953), the patient has continued to do well on daily doses of cortisone and periodic injections of long-active desoxycorticosterone preparations intramuscularly. The original dose of cortisone was 12.5 mg. daily; in September, 1952, it was increased to 18.75 mg. daily. Desoxycorticosterone phenylacetate was given intramuscularly in dosage of 60 mg. every six weeks until early in 1952. Since then, desoxycorticosterone trimethylacetate [47] has been administered in like amount every 30 days.

The patient progressed well and took part normally in activities at the Elliott P. Joslin Camp for diabetic boys, both in 1952 and in 1953. During the two years, the insulin requirement varied widely, from 25 to 44 units daily. However, since the patient's adherence to diet under home conditions is variable, it is difficult to interpret shifts in insulin requirement. In general, the degree of control of diabetes has been fair and is not unlike that of many juvenile diabetics.

In December, 1952, the patient was treated at another hospital for acute gastroenteritis. Because of his unusual weakness and lethargy, it was thought that an Addisonian crisis was

TABLE 3.—*Results of Eosinophile Tests and 17-Ketosteroid Determinations in Case 1 (A. C.; Case 46 in Table 1)*

Date, 1951	Substance Administered	Dose, Mg.	Route *	Eosinophiles in Circulating Blood, No./Cu. Mm.		% Change	17-Ketosteroid Excretion in Urine, Mg./24 Hr.
				Initial	Final		
6/14	Epinephrine	0.25	S. C.	42	87 †	+107	....
6/22	Epinephrine	0.25	S. C.	113	203 †	+ 80	....
6/25	Corticotropin	25	I. M.	156	300 †	+ 93	0.34
6/29	Corticotropin	20	I. V.	519	381 ‡	— 28	0.35
7/11	Corticotropin	20	I. V.	563	188 ‡	— 67	0
7/12	Corticotropin	20	I. V.	406	544 ‡	+ 34	0
7/13	Corticotropin	20	I. V.	567	581 ‡	+ 2	0.25±

* S. C., subcutaneous; I. M., intramuscular; I. V., intravenous.
† Final eosinophile count made four hours after injection.
‡ Final eosinophile count made after continuous intravenous infusion of corticotropin for eight hours (except for test of July 12, when time was six hours).

impending. He was able to leave the hospital in four days after treatment with insulin, salt solution intravenously, antibiotics, and additional cortisone.

From October, 1951, to September, 1953, his height increased from 132 cm. (52 in.) to 142 cm. (56 in.) and his weight (dressed without shoes) from 31.2 kg. (63¾ lb.) to 34.1 kg. (75 lb.). On Sept. 4, 1953, the heart, lungs, and abdomen seemed normal and the blood pressure was 100/60.

CASE 2.—K. H. (Case 43 * in Table 1) was first seen at the New England Deaconess Hospital on March 14, 1934, at the age of 27.8 years. She had been in good health until January, 1934, when weight loss, polydipsia, and polyuria developed. Glycosuria was first found shortly before admission. There was no family history of diabetes mellitus. Initial physical examination gave findings within normal limits; the blood pressure was 130/80. The patient weighed 54.5 kg. (120 lb.) and was 165.7 cm. (65¼ in.) tall. Urinalysis showed 0.5 to 2% sugar; it was otherwise normal, except for a slight trace of albumin. Blood sugar values ranged from 230 mg. to 90 mg. per 100 cc. (after insulin therapy had been started). The patient was given a diet of carbohydrate 150 gm., protein 75 gm., and fat 85 gm. per day. She was discharged on the 11th hospital day, on a total of 42 units of crystalline insulin daily.

Thereafter, she was seen at office visits at intervals of one to six months. Random blood sugar values ranged from 100 to 265 mg. per 100 cc. The insulin dosage was gradually decreased

* Previously reported by Thorn and co-workers.[42]

to 28 units daily. In July, 1937, she was shifted to protamine zinc insulin and her condition was regulated on 10 units of crystalline and 36 units of protamine zinc insulin, given by separate injection daily before breakfast. In June, 1938, the patient became pregnant; from December, 1938, to her delivery, in March, 1939, she was seen at office visits twice weekly. After delivery of a normal female child, the patient did not lactate; her postpartum course was otherwise uneventful. After this, she was seen at office visits from time to time. In March, 1947, she was taking 6 units of crystalline and 25 units of protamine zinc insulin daily.

When seen in March, 1949, it was noted that her skin was deeply tanned and showed multiple dark freckles. The patient's only complaints at this time were slight fatigue and frequent upper respiratory infections. In April she was transferred to isophane insulin, 28 units daily. She was hospitalized in August, 1949, because of marked fatigue and weakness, as well as frequent insulin reactions despite the reduction of her daily dose to 18 units. Her intense tan was of approximately 18 months' duration. During the preceding nine months, a gradual loss of pubic and axillary hair had taken place; there had been no change in libido. She had been amenorrheic for two months. There was no salt craving. She now weighed 53.4 kg. (117½ lb.). Physical examination revealed a blood pressure of 82/60 to 104/70. The skin showed marked pigmentation, with many dark freckles; the buccal mucosa was also pigmented. Studies showed a blood hemoglobin of 11.2 gm. per 100 cc. and a red blood cell count of 3,580,000. Roentgenograms of the chest and abdomen were normal. An electrocardiogram showed low voltage. The blood chloride was 98 mEq. per liter. The basal metabolic rate was +4%, and a 38% decrease in eosinophiles followed epinephrine administration. Eleven days after she was started on sodium chloride intravenously and orally, the patient began to menstruate, after a three months' period of amenorrhea. She was discharged on a diet of carbohydrate 182 gm., protein 91 gm., and fat 114 gm., with supplemental salt (3 gm. daily) and 20 units of isophane insulin daily.

In October, 1949, she was admitted to the Peter Bent Brigham Hospital.† The results of laboratory studies while she was there were hemoglobin, 9.2 gm. per 100 cc.; red blood cell count, 2,970,000; hematocrit level 29%; total protein, 4.9 gm. per 100 cc.; CO_2, 22.5 mEq. per liter, and cholesterol, 161 mg. per 100 cc. Electrolyte determinations were as follows: chloride, 106 mEq.; sodium, 146 and 143 mEq.; potassium, 4.3 and 4.5 mEq. per liter. The basal metabolic rate was + 9%; radioactive-iodine-uptake gave a gradient of 7 (normal, 1 to 10). Four-hour tests with epinephrine and corticotropin showed a 33% fall and 6% rise, respectively, in the level of circulating eosinophiles; a 48-hour corticotropin test gave a fall in eosinophiles from 166 to 79. Excretion of 17-ketosteroids in the urine was 2.2 mg. per 24 hours; it fell to 1.4 mg. on corticotropin therapy. An electrocardiogram showed low voltage and prolonged QT interval; an electroencephalogram was mildly slowed. During the hospital stay, on one occasion hypoglycemia followed administration of only 5 units of insulin, precipitating a mild Addisonian crisis. She was discharged on a diet of carbohydrate 185 gm., protein 100 gm., and fat 100 gm., with 15 units of isophane insulin daily; other daily medications included 5 mg. of cortisone intramuscularly, 0.5 cc. of desoxycorticosterone acetate (Percortin), 3 gm. of sodium chloride, ferrous gluconate, conjugated estrogenic substances (Premarin), and rutin. In December, 1949, desoxycorticosterone acetate (DOCA) (375 mg.) and cortisone (234 mg.) pellets were implanted; this was repeated in May, 1950. In September, 1950, she was placed on cortisone orally with continued desoxycorticosterone acetate implantation. In January, 1952, she was shifted to trimethyl desoxycorticosterone acetate (Ciba) (45 mg. every six weeks, intramuscularly), with continuance of cortisone (37.5 mg. daily) orally. The patient was feeling well on a daily insulin dosage of 36 units.

Subsequent Course.—Since 1952, the patient has continued to do well. When last studied at the Peter Bent Brigham Hospital, in June, 1953, treatment included the following: diet of carbohydrate 180 gm., protein 100 gm., and fat 100 gm. daily; insulin, 34 units isophane insulin daily; cortisone, 12.5 mg. twice daily, and desoxycorticosterone trimethylacetate, 60 mg. intramuscularly at monthly intervals.

† Dr. George W. Thorn and associates provided the data from the Peter Bent Brigham Hospital.

COMMENT

The studies here reported emphasize that although diabetes mellitus and Addison's disease only rarely occur in the same patient the clinical features are characteristic and recognition is important, since with modern therapy both conditions can be successfully treated and useful life made possible. Forty-six patients, 26 males and 20 females, have been reported to date. All but four have been recognized in the insulin era. The average age at the time of recognition of the coexistence of the diseases was 37.7 years, with extremes of 10 and 69 years of age. The average age at death (or at last report) was 41.7 years. The duration of diabetes at death (or at last report) averaged 6.9 years, and that of Addison's disease, 3.0 years. Thus, one deals primarily with diabetes complicated by Addison's disease, rather than the reverse. In only 11 cases was it reported that Addison's disease preceded diabetes; in 3 other patients the onset of the two conditions seems to be at about the same time.

As is well demonstrated in the two cases here presented in detail, Addison's disease developing in a diabetic is characterized by a diminution in the insulin requirement, with frequent hypoglycemic reactions. Weakness, fatigue, and, as in Case 1, Addisonian crises with characteristic electrolyte changes may supervene. In the differential diagnosis one must consider hypopituitarism, hypothyroidism, and disorders of the liver.

The therapeutic problem posed by the coexistence of these two conditions is by no means insurmountable. Each is treated definitively with the appropriate substitution therapy. In combination with cortisone given orally, long-acting desoxycorticosterone acetate (DOCA) preparations for intramuscular administration are especially useful.[47] Unusual care must be taken in the presence of stress, such as infections and acidosis. It is to be hoped that by prolongation of life by careful treatment not only will patients benefit directly but greater understanding of the fundamental nature of both diseases may be obtained by observation of their interaction over years of time.

ADDENDUM

In 1953 Breslaw, Lashof, and Klein [48] reported another case in which diabetes mellitus and Addison's disease coexisted, thus bringing the total published cases now to 47. Their patient was a woman in whom the diagnosis of diabetes and hyperthyroidism was established at the age of 48 years and that of Addison's disease four years later.

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PRIMARY HEMOPHILUS INFLUENZAE PNEUMONIA

Report of Four Cases

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WHILE other types of infections with Hemophilus influenzae, such as meningitis and upper respiratory disease, are rather frequently seen, primary H. influenzae pneumonia is a relative rarity. A survey of the American literature published during the past 20 years regarding this type of pneumonia revealed only three case reports.

In view of the paucity of available information regarding the treatment of this variety of pneumonia, it was thought that our experience with the chemotherapy of four patients with primary H. influenzae pneumonia should be reported.

Since 1946, approximately 3,600 patients with pneumonia of all kinds have been treated at the District of Columbia General Hospital. Of this group, H. influenzae has been proved to be the primary etiologic agent in only four. The treatment of these patients varied according to the availability of the chemotherapeutic agents and was dependent upon investigative work being carried on at the time of their respective admissions.

REPORT OF CASES

CASE 1.—B. C., a 30-year-old Negro maid, had been a known diabetic for four years, maintained on 15 units of protamine zinc insulin daily until two years prior to admission, since which time the diabetes had been controlled with diet alone. She was well until the day prior to admission, when she noted fatigue, anorexia, and multiple joint pains. Later she developed a shaking chill, profuse sweating, and a mild cough, followed after several hours by severe right anterior chest pain, aggravated by respiration and coughing. During that night she experienced repeated chills and sweats; the cough became productive of rusty sputum.

There was a past history of bilateral "pleurisy" in 1943, untreated.

Upon admission to the District of Columbia General Hospital, on Nov. 24, 1952, the patient appeared acutely ill, dyspneic, and orthopneic and complained of severe chest pain. The temperature was 101.8 F., pulse rate 100, respiratory rate 40, and blood pressure 140/92. The significant findings were confined to the chest. There was limited expansion of the right hemithorax. Dullness, increased breath and voice sounds with "E to A" change, and moist inspiratory rales were found over the lower half of the right anterior lung field. Urinalysis revealed 4+ sugar and 4+ acetone. The white blood cell count was 12,000, with 49% segmented neutrophiles,

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30% band cells, 7% young forms, 13% lymphocytes, and 1% monocytes. The blood sugar was 216 mg. per 100 cc.; CO_2-combining power was 46.4 vol. %. The serological test for syphilis (VDRL) was negative.

Roentgenogram of the chest (Figs. 1 and 2) showed extensive pneumonitis involving the right middle and lower lobes. Sputum and blood specimens were sent to the laboratory for culture.

The diabetic acidosis was treated with frequent injections of regular insulin and intravenous saline infusions. Erythromycin, 300 mg. per os every four hours, was given for two days. The patient remained toxic and orthopneic and had marked difficulty in raising the sputum, which was viscid and grossly hemorrhagic. In view of the lack of improvement with erythromycin and the recurrence of acetonuria, it was decided to discontinue this agent. Aqueous penicillin procaine, 600,000 units intramuscularly every 12 hours, was given until the fourth hospital day, at which time the sputum and three blood cultures taken on admission were reported positive for H.

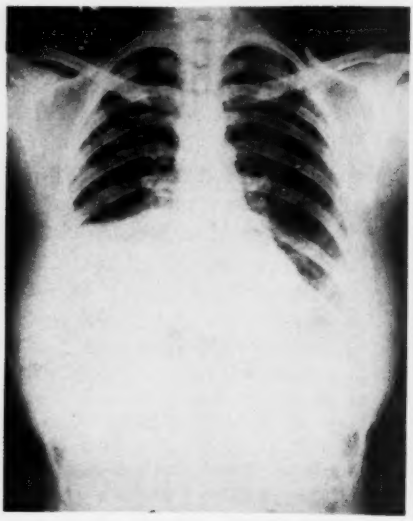

Fig. 1 (Case 1).—Posteroanterior roentgenogram of the chest taken on admission, showing extensive pneumonitis involving right middle and lower lobes.

Fig. 2 (Case 1).—Right lateral roentgenogram of the chest taken on admission.

influenzae, Type B. Since the clinical state and roentgenogram remained essentially unaltered, the chemotherapy was changed to 1 gm. of streptomycin intramuscularly every 12 hours and 500 mg. of oxytetracycline (Terramycin) intravenously every 4 hours.

On the sixth hospital day the patient experienced a shaking chill. The white blood cell count was 16,050, with 85% neutrophiles. Blood cultures drawn at this time were subsequently reported sterile. Increasing difficulty with intravenous injections of oxytetracycline made substitution by oral administration necessary.

By the 10th hospital day the patient was afebrile, with pulse rate 80, respiratory rate 20, and white blood cell count 7,650, with normal differential count. Chest x-rays demonstrated considerable resolution of the pneumonia.

Two days later, streptomycin was reduced to 1 gm. daily and oxytetracycline to 500 mg. every six hours.

The streptomycin was discontinued on the 17th hospital day, and oxytetracycline was stopped two days later. The patient remained afebrile and was discharged asymptomatic, on Dec. 18, 1952, her diabetes well controlled on a dose of 20 units protamine zinc insulin daily. Chest x-ray at the time of discharge showed almost complete resolution. A follow-up roentgenogram two months later (Fig. 3) revealed only a slightly thickened pleura.

CASE 2.—R. W., a 31-year-old Negro woman, a chronic alcoholic, had been hospitalized numerous times between 1946 and 1951 for Laennec's cirrhosis, gastroenteritis, and recurrent bouts of pancreatitis. One month before admission she had been treated with penicillin for a cellulitis of the left leg. Ten days before hospitalization she had sustained a knife wound of the left side of the neck requiring 10 sutures.

The present illness began one week before admission with coryza and nonproductive cough, followed in a few days by aching in the knees and shoulders, nausea, vomiting, diarrhea, and

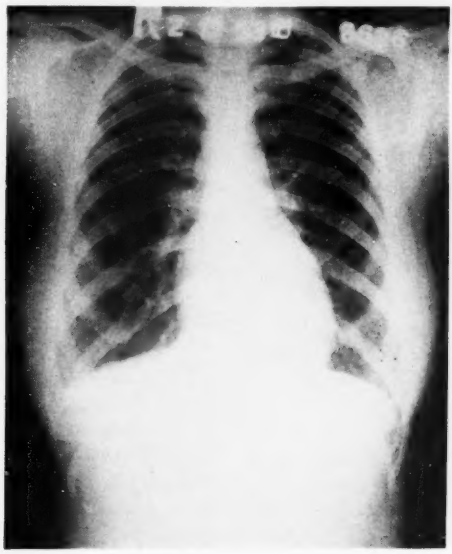

Fig. 3 (Case 1).—Roentgenogram of the chest taken two months after discharge from hospital.

anorexia. The shoulder pain was aggravated by motion and deep breathing. A shaking chill, high fever, and shortness of breath occurred on the morning of admission, Nov. 1, 1951.

Physical examination disclosed a thin malnourished tachypneic woman complaining of pain in the legs and shoulders, with temperature of 101 F., pulse rate 110, and blood pressure 80/50. There were a healing sutured wound on the left side of the neck and a chronic encrusted ulcer on the left leg. Dehydration was evident. Over the left lower lung field posteriorly bronchial breath sounds with increased spoken and whispered voice sounds were heard. No rales were audible. The liver was enlarged to 6 cm. below the right costal margin.

The white blood cell count on admission was 4,800, with 65% neutrophiles, 33% lymphocytes, and 2% monocytes. The hematocrit reading was 38%. Urinalysis was essentially negative. X-ray of the chest (Fig. 4) revealed a homogeneous density in the lateral portion of the right upper lobe, with increased density at both bases, consistent with pneumonia.

On the second hospital day, aqueous penicillin procaine, 600,000 units intramuscularly every 12 hours, was started. The following day the patient was noted to have right pleuritic pain,

with rales at the right base posteriorly but no other signs of consolidation. On the fourth day extreme tenderness over the lower right axillary region was observed.

The patient remained toxic and was irrational at times. The fever persisted, and the pulse rate varied from 90 to 140. On the fifth hospital day the three blood cultures taken on admission were reported as showing H. influenzae, Type B. Sputum culture had yielded no significant pathogens. The white cell count was 19,000; hemoglobin, 7.8 gm. per 100 cc., and hematocrit reading 29%.

At this time penicillin was discontinued and chloramphenicol (Chloromycetin) was started, with an initial dose of 1 gm. intravenously and 0.5 gm. orally, followed by 0.5 gm. orally and 0.5 gm. intravenously every four hours. On the following day the intravenous injections were replaced by intramuscular administration; oral doses were continued. Twenty-four hours after

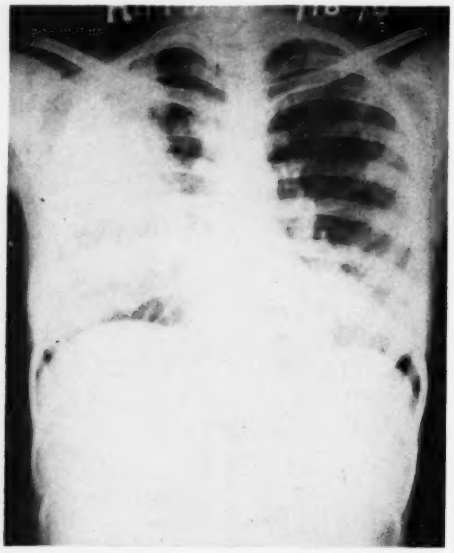

Fig. 4 (Case 2).—Posteroanterior roentgenogram of the chest taken on admission, showing homogeneous density in the lateral portion of the right upper lobe, with increased density at both bases, consistent with pneumonia.

initiation of chloramphenicol therapy improvement was noted, with a diminution in toxicity and chest pain. The roentgenographic picture at this time remained essentially the same as on admission.

On the ninth hospital day the intramuscular dosage of chloramphenicol was reduced to 0.5 gm. every six hours instead of every four hours. By the 10th hospital day, the temperature was 99 F. Gradual improvement in the pneumonia was evident clinically and roentgenographically. Intramuscular chloramphenicol was discontinued on the 16th hospital day. By the 25th day the white blood cell count had returned to normal levels. X-ray showed further clearing, and oral administration of chloramphenicol was stopped.

The patient was discharged afebrile and asymptomatic after 33 days of hospitalization.

Case 3.—E. A. B., an 11-month-old white girl, was well until five days before admission, when she became feverish and refused food. Despite symptomatic treatment by a local physician the temperature rose to 105 F. on the following day, and pallor, cyanosis, and rigors were

observed. Three days before admission the temperature remained at 105 F. and several "pimple-like" lesions were noted on the knees and elbows. At this time blood cultures were drawn by the private physician. The following day the temperature reached 107 F., and the physician prescribed sulfadiazine, 0.5 gm. per kilogram as an initial dose and 1.0 gm. per kilogram per day, divided into six doses.

The temperature declined, but on the day of admission it rose to 103 F. On this day the blood culture was reported as positive for H. influenzae, Type B, and the infant was admitted to the pediatric division of the District of Columbia General Hospital, on March 20, 1947.

Physical examination disclosed a temperature of 103.6 F. Several pin-point macules were observed on the elbows and knees. There were redness, thickening, and distortion of landmarks of the right tympanic membrane, and the anterior fontanelle appeared to bulge slightly. There were no other significant physical findings.

White blood cell count was 10,000, with 72% lymphocytes. Cerebrospinal fluid was normal. Chest x-ray showed "diffuse mottling at the right base most likely due to pneumonitic infiltration."

Streptomycin administration was started immediately, 250 mg. intramuscularly every three hours. On the day after admission definite signs of consolidation were elicited over the middle one-third of the right chest posteriorly. Penicillin was added to the chemotherapy on the second hospital day, 30,000 units intramuscularly every three hours. The temperature response was gradual, reaching normal on the sixth hospital day. Cultures of blood and cerebrospinal fluid made at the time of admission were reported sterile. Streptomycin was discontinued on the fifth hospital day, and penicillin was stopped on the ninth day. Recovery was uneventful, and the patient was discharged after 10 days of hospitalization.

CASE 4.—J. C., a 69-year-old Negro man, was admitted to the District of Columbia General Hospital on March 3, 1953. He had been well until six days previously, when he awakened with generalized aching. A cough productive of rather copious yellowish, occasionally blood-tinged, sputum and right pleuritic pain appeared during the ensuing day and persisted until hospitalization. He denied fever, chills, or severe sweating. There was a transient ankle edema.

Previous history included pneumonia 40 years ago, with no other significant illnesses.

At the time of admission the patient was dyspneic and coughing and appeared acutely ill and moderately dehydrated. The temperature was 102 F., pulse rate 120, respiratory rate 44, and blood pressure 122/72. The pharynx did not appear inflamed, but a purulent sputum was seen covering the mucous membranes. There was splinting of the right chest; diminished tactile fremitus, dullness, and fine crackling inspiratory rales were found over the right lower posterior lung field. "E to A change" was heard throughout both lung fields, anteriorly and posteriorly, except over the extreme right base posteriorly and laterally. Crackling rales were heard also over the right middle lobe anteriorly. The remainder of the physical examination was not remarkable except for slight pretibial edema.

Initial hematocrit reading was 34%; white blood cell count was 16,500 (48 hours later WBC count was 22,250, with 64% neutrophiles, 30% band cells, and 6% lymphocytes); urinalysis showed 1+ albumin, with many red blood cells and many red blood cell casts. Roentgenogram of the chest showed a homogeneous infiltration involving the lower half of the right lung field and the lower two-thirds of the left lung field.

Direct smears of the sputum demonstrated many Gram-positive cocci in short chains.

A thoracentesis of the right chest yielded only a few cubic centimeters of yellowish serous fluid. This fluid, with the sputum and three blood samples, was sent to the laboratory for bacteriologic study.

Initial therapy consisted of erythromycin, 300 mg. every four hours for six doses and then 100 mg. every four hours, with potassium iodide, nasal oxygen, and the usual supportive measures. This therapy was maintained for three days, during which period the manifestations of acute illness and toxicity continued, with minimal temperature response and persistence of the marked leucocytosis.

On the third hospital day, the three admission blood cultures and the fluid obtained by thoracentesis were reported to have grown H. influenzae, "Type other than A or B"; one sputum sample was reported on culture as containing Group F, Type 23 Pneumococcus, "and a few Gram-negative rods."

At this time, erythromycin was discontinued, and oxytetracycline therapy was instituted, 500 mg. intravenously followed by 500 mg. orally every six hours. On the sixth hospital day the hematocrit level was noted to be 22%, and 1,000 cc. of whole blood was administered. The intravenous oxytetracycline was stopped, and 250 mg. of oxytetracycline (with 20 cc. of a proprietary gastric antacid [Gelusil] because of vomiting) was given by mouth every three hours.

X-ray at this time showed clearing of the density in the left midlung field.

The temperature slowly diminished, reaching a normal level on the eighth hospital day, five days after oxytetracycline had been started. Clinical and x-ray findings indicated a gradual resolution of the pneumonia. On the 13th hospital day the white blood cell count had reached 8,450 and the hematocrit level was 34%.

After 16 days of oxytetracycline administration, this drug was discontinued. Recovery continued uneventfully, and the patient was discharged after 23 days of hospitalization.

COMMENT

The clinical features demonstrated by these four patients with proved H. influenzae pneumonia were essentially similar to those accompanying most lobar pneumonias. However, it is noteworthy that each of our three adult patients experienced severe generalized musculoskeletal pains as a prominent symptom early in the course of his illness. While this observation may be coincidental, this symptom seems to have occurred frequently enough to bear mentioning.

It is usually stated that pneumonia caused by H. influenzae is bronchopneumonic in distribution.[2] It is of interest that in all of our cases the distribution was lobar in type, indistinguishable roentgenographically from other lobar pneumonias.

Chemotherapy was instituted in each instance before bacteriologic diagnosis was established. Cases 1 and 4 received erythromycin initially, Case 2 was given penicillin, and Case 3 received sulfadiazine all in dosages which are generally considered adequate for treatment of the most commonly encountered pneumonias. Only after the results of blood and sputum cultures were obtained were the broad-spectrum antibiotics employed. A combination of streptomycin and oxytetracycline was utilized in Case 1, chloramphenicol alone was employed in Case 2, Case 3 received penicillin along with streptomycin, while in Case 4 oxytetracycline alone was administered. In each instance, the administration of streptomycin and/or a broad-spectrum antibiotic was successful in controlling the infection.

Since H. influenzae is a Gram-negative organism, it is readily apparent that penicillin and erythromycin alone would be ineffective. The routine use of admission blood cultures, by providing a specific bacteriologic diagnosis, allowed the adoption of appropriate chemotherapy early in the course of treatment.

Blood cultures taken before institution of chemotherapy in our four cases may well be credited with having prevented such serious complications as meningitis and empyema and even a fatal outcome.

Our experience with these four cases indicates that H. influenzae pneumonia may be adequately treated, and with apparently equal effectiveness, by streptomycin, oxytetracycline, or chloramphenicol. The emergence of resistant organisms during

specific chemotherapy of H. influenzae infections has been reported [3]; consequently, sensitivity studies should be employed when adequate response to chemotherapy is not obtained.

SUMMARY

Primary Hemophilus influenzae pneumonia is rare, occurring in less than 0.1% of all pneumonias in our hospital since 1946.

Four case reports are presented, three of adults and one of an infant, with details of chemotherapy.

All four cases showed a lobar distribution, rather than the bronchopneumonia usually associated with H. influenzae infection of the lungs.

Oxytetracycline (Terramycin), streptomycin, and chloramphenicol (Chloromycetin) are apparently equally effective in treatment.

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USE OF "DIBENZYLINE" AS A VASODILATOR IN PATIENTS WITH SEVERE DIGITAL ISCHEMIA

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IN THE management of patients with vascular disease one naturally seeks for a vasodilator drug which will offer substantial vasodilatation in the extremities with minimal effects elsewhere. Such a drug would be particularly useful in so-called Raynaud's syndrome, where it might often obviate the need for surgical sympathectomy, especially for the upper extremity, when the operation is frequently unsatisfactory.

The vasodilator effect of Dibenzyline * (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride) has been briefly reported by several observers.† The results in a few patients in whom we tried this drug in 1951 gave promise that Dibenzyline more nearly approached the ideal than other vasodilators with which we were acquainted. This opinion was strengthened by a further use of Dibenzyline over a two-year period for 23 patients suffering from severe digital ischemia, and we, therefore, offer this account of our experiences. We feel that the drug was given a somewhat more rigorous test than it had received in previous clinical trials, because of the severity of the disease process in our patients, most of whom exhibited ischemic ulceration of the tips of the fingers or toes.

PHARMACOLOGY

Dibenzyline is one of a series of compounds related to Dibenamine (N,N-dibenzyl-β-chloraethylamine), whose major characteristic is their ability to block adrenergic impulses.[8]

Dibenzyline is active both intravenously and orally, oral doses being given as capsules of the powdered drug. When it is given intravenously in a dose of 50 to 75 mg., significant adrenergic blockade is produced in 30 to 40 minutes. After oral administration, effects are noted in 1 to 2 hours, continuing in full force for 3 to 6 hours, with minimal effects noted for as long as 12 hours.[9]

The effects on the blood vessels, especially of the periphery, are most striking. Woodward and co-workers [6] noted that peripheral blood flow was increased as much as 500% after intravenous injection in both normal and hypertensive subjects.

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* Dibenzyline is a trademark of Smith, Kline & French Laboratories.

† References 1-7.

Persons with peripheral arterial disease showed much less increase. He thought the increase in peripheral blood flow to be equal to that produced by anesthetic block of the sympathetic trunks and to be twice as great as that produced by tetraethylammonium chloride.

Skin temperatures of the hands and feet are greatly increased. Haimovici [4] found elevations of 1 to 15 F., which were most pronounced about one and one-half hours after oral administration. As with other forms of sympathetic blocks, sweating is diminished and, indeed, is absent from the extremities.

The vasodilatation results in a hypotension, especially in the erect posture. The pressure often falls 15 to 20 mm. mercury, the systolic pressure being somewhat more affected than the diastolic. A dose of 40 mg. orally, three times a day, produced postural hypotension in 8 out of 15 patients studied by Redisch.[10] Haimovici and co-workers observed postural hypotension in all of 47 patients they studied and observed a greater fall in hypertensive than in normotensive subjects.[11]

While Dibenzyline acts predominantly on the sympathetics of the periphery, it affects the other territories of this system as well, but to a lesser and varying degree. Tachycardia and palpitation occur reflexly in patients exhibiting postural hypotension, but they may be noted in the absence of significant blood pressure effect. Renal function is unaltered, according to Ford and Moyer.[12] Contraction of the pupil and loss of convergence, with blurring of vision, often appear and are helpful in indicating adequacy of dosage. The eye signs may not appear for one to three days. Vasodilatation in the nasal mucosa is a quite constant effect, resulting in a "stuffy" feeling and, rarely, in epistaxis. There is minimal effect on the gastrointestinal tract, patients rarely experiencing slight epigastric distress. The bladder is unaffected, but some genital effects may be noted. Male patients receiving 50 to 120 mg. a day for several weeks may show some decrease or absence of ejaculated semen, although libido and potency are undiminished.[13] Irregularity of menses occasionally develops in women.[9]

The effect of Dibenzyline after a single dose is considerably reduced after 6 hours and is nearly gone in 12 hours. Haimovici [4] and Bakke and Williams [14] noted the development of tolerance to Dibenzyline after variable periods of time from a few weeks to several months. This, however, was not a problem in our cases, and we observed a good effect on peripheral circulation after periods of six months or more. In no patient did we observe any marked degree of resistance to the drug. After a patient has been on the drug several days, the effect persists for as long as 24 to 48 hours.

CLINICAL EXPERIENCE

Patients.—A total of 23 patients with digital ischemia have been treated with Dibenzyline. The diseases represented are summarized in the Table. Fourteen suffered from what may be termed true Raynaud's disease, that is, a chronic disorder characterized by severe paroxysms of digital ischemia on exposure to cold. While the pathology of this disease is uncertain, spasm is, at least, the predominant mechanism of the ischemia. In our patients the malady had existed for many years; it troubled them mainly in the winter, and complete history and physical examination failed to indicate the presence of any other disease to which the vasospasm could be considered secondary. Certain laboratory procedures were done to assist in identifying these diseases. These procedures included in each case a search for cold agglu-

tinins and cryoglobulin and, in selected cases, a basal metabolism test to rule out hypothroidism; determination of the albumin-globulin ratio, relating especially to scleroderma, and biopsy of the tips of the affected fingers and toes.

In the course of these examinations, nine patients were found whose ischemia was caused by diseases other than Raynaud's disease. Among these were four cases of remittent necrotizing acrocyanosis. In each of the 23 patients, organic occlusion of large or small vessels is either certainly or probably the basic fault. In nine patients Dibenzyline was used as the major therapy; in others the drug was but part of the treatment.

The designation "remittent necrotizing acrocyanosis" deserves explanation. This term denotes a disorder characterized by symmetrical cyanosis and coldness of the hands or feet, with necrosis of the tips of the fingers or toes; the malady appears suddenly in late adult life, without regard to season, in attacks of some months' duration, usually ending in spontaneous remission but with a tendency to recur.

Results of Treatment with Dibenzyline

Disease	Results of Treatment: Satisfactory	Results of Treatment: Unsatisfactory
A. Predominantly vasospastic (15 patients)		
Raynaud's disease, including 4 with necrosis	14	..
Minor causalgia	..	1
B. Certainly or probably organic (8 patients)		
Remittent necrotizing acrocyanosis	3	1
Early scleroderma	1	..
Postembolic ischemia	1	..
Obstruction of major artery by probable hematoma	1	..
Arteriosclerosis with residual sympathetic activity after operation	..	1

Thrombosis of small vessels of the digits is, at least sometimes, responsible. A group of 20 cases, including the 4 treated with Dibenzyline, is being reported elsewhere.

Dosage and Side-Effects.—The drug was given orally in capsules varying in size from 5 to 20 mg. One such capsule was given one to four times a day, the total daily dosage, therefore, varying from 5 to 80 mg.

Nasal stuffiness was a constant side-effect but was never troublesome enough to force the patient to discontinue treatment. Occasionally, epistaxis of mild degree occurred in patients with severe nasal obstruction. Dizziness, weakness, and nausea were occasionally observed and often accompanied postural hypotension. These caused one patient to discontinue treatment, but her disease had abated considerably. Serious syncope is easily controlled by placing the patient in a recumbent position and elevating the lower extremities. Several patients complained of feeling sleepy; one complained of blurring of vision, and one man noted failure of ejaculation on intercourse, although orgasm was experienced. Tachycardia was frequently noted but presented no serious problem in our cases.

Most of these symptoms diminished after the patient had been on treatment a few days. The nasal congestion was fairly well relieved by the topical application of 0.25% phenylephrine hydrochloride nose drops or by sniffing a propylhexedrine (Benzedrex) inhaler. It was not relieved by antihistaminic drugs. The drowsiness was overcome by the use of dextro-amphetamine. Once vasodilatation was estab-

lished, the dose of Dibenzyline could be reduced to perhaps 5 mg. every eight hours with fair maintenance of therapeutic effect but with reduction of the side-effects. Another helpful maneuver was to give the patient one large dose, for example, 20 mg., on retiring. Side-effects would then pass unnoticed, while the peripheral vasodilatation would often persist through the next day.

Results.—Marked benefit resulted in those patients whose disease was marked mainly by vasospasm (Table). All the patients with true Raynaud's disease experienced a gratifying warmth of the hands and feet, with loss of the paroxysms of vasospasm and relief from pain due to ulcerations of the finger tips and healing of these lesions. Similar relief was also obtained in several patients in whom organic disease of fine vessels was present, such as the patient with early scleroderma (Case 4), and in three of the four patients with remittent necrotizing acrocyanosis. The only examples of failure of the Dibenzyline to give satisfactory relief of the ischemia were found in the patients with organic disease of the vessels.

REPORT OF CASES

CASE N52J6 (I. L.).—*Raynaud's Disease; Satisfactory Control with Dibenzyline*

A 47-year-old married woman was seen in July, 1952, at which time she was complaining of pain in the index finger of the right hand, which had suddenly turned white after the handling of a glass full of ice cubes. She had noted that the fingers of both hands had, on occasions when they were exposed to cold water, been blanched white and that the right index finger had become blue. Prior to this time she had had no difficulty with exposure to cold.

On examination, the hands were cold, and the right index finger, during the course of the examination, turned white as far as the second interphalangeal joint. There was also blanching of the ring and, to a less extent, the middle and little fingers on this hand. After approximately 15 minutes the white blanching faded, to be replaced by a light bluish color. At the extreme tip of the right index finger there was a small area of ulceration, which was exquisitely tender when palpated. There was blueness of the fingers on the left hand, but no real blanching could be seen (Fig. 1). She was immediately started on Dibenzyline, 20 mg. three times a day after meals.

After two weeks she was examined; the hands were definitely warmer, and there was already evidence of healing in the right index finger. Some skin could be seen peeling from the tip of this digit. She complained of mild nasal stuffiness but otherwise had no troublesome symptoms. She said that the pain had left the fingers but that if she put her hands in cold water the white blanching would return.

During the next three months, while on Dibenzyline, 20 mg., four times a day, she had complete healing of the ulcerated lesion and was able to continue her ordinary activities without too great discomfort. Blanching, however, did recur on rare occasions when the hands were exposed to cold or she was subjected to severe emotional stress. She, however, remained completely free of pain, and the old ulcerated area healed and remained so. Gradually, the dose of Dibenzyline was reduced to 5 mg., four times a day, and she has had very little difficulty with her vasospastic disease during the past winter and up until the summer of 1953. She finds, however, that she must continue the drug, since on one or two occasions she found that when she was not taking Dibenzyline, the spasms returned and tended to be far severer.

CASE 8E319 (M. Mc.).—*Raynaud's Disease with Necrosis of Finger Tips; Healing with Dibenzyline*

A 31-year-old woman was seen in February, 1952, complaining of subungual infections and painful "cracks" of the finger tips. For 10 years, attacks of numb, white fingers had occurred on exposure to cold. For four years the finger tips had undergone "cracking" each winter.

On examination, the fingers were cold, sweaty, and cyanotic. The cyanosis extended to the forearm. The fingers tapered, with loss of the distal creases. Spots of necrosis and puckered scars from previous necroses could be seen on the atrophied finger-tip pads (Fig. 2). The radial

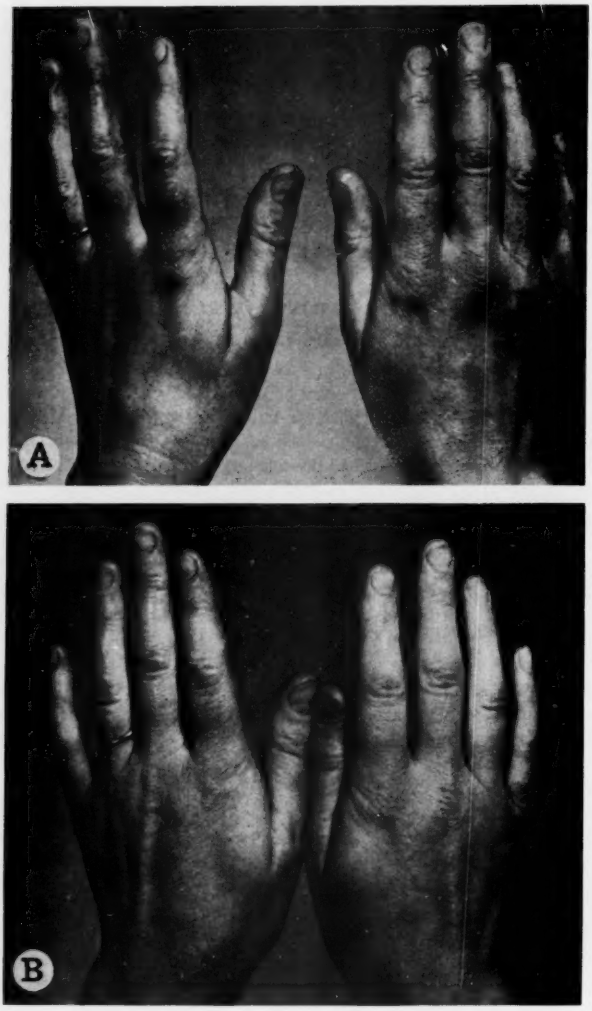

Fig. 1 (Case N52J6).—*A*, mottled cyanosis and blanching after chilling in a patient with Raynaud's disease. *B*, absence of vasospastic reaction during Dibenzyline treatment.

pulses were of good quality. X-ray showed diminution of the tufting of the distal ends of the terminal phalanges. Biopsy of a finger tip showed agglutinative thrombi in several capillaries of the dermis. The remainder of the physical and laboratory examination was not remarkable.

Twenty milligrams of Dibenzyline were given twice a day. The patient experienced gratifying warmth and comfort of the fingers. She found it possible to go out in the cold with only one pair of thin gloves instead of three pairs of mittens she previously wore. By April, 1952, all symptoms had abated and the drug was discontinued.

Symptoms recurred the following September, and 60 mg. of Dibenzyline a day were required to relieve the pain. By late November the finger tips healed (Fig. 2*B*), but she felt drowsy and could not get her work done. This symptom was relieved by reducing the dose of the drug to 20 mg. a day and giving 5 mg. of dextro-amphetamine twice a day. With this regimen she went through the rest of the second winter without further difficulty.

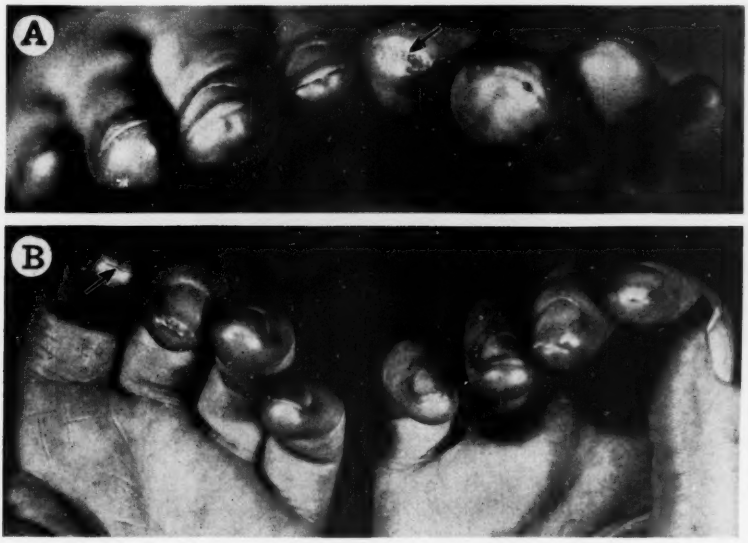

Fig. 2 (Case 8E319).—*A*, ulceration of finger tips and scarring from old attacks in a patient with Raynaud's disease. *B*, healing after Dibenzyline treatment. Arrow indicates fresh ulcer on left index finger.

Case P4811 (M. D.).—*Minor Causalgia of Hand; Myxedema; Failure of Dibenzyline*

A 44-year-old man accidentlly closed the door of a truck on the fingers of the right hand. The contusion was severe, but there was no fracture. Extreme pain in the hand, with marked hyperesthesia, coldness, and cyanosis resulted. Severe myxedema had been present for three years. He was not taking thyroid at the time of the injury, although a typical marked myxedema was present, with a basal metabolic rate of — 40%. The coldness and edema of the extremities were much accentuated in the injured hand.

Several stellate ganglion blocks had been done with equivocal results. Five months after the injury he was given 10 mg. of Dibenzyline three times a day. This was discontinued after one week because no relief was experienced. The symptoms were finally controlled by a procaine block of the wrist and two more stellate ganglion blocks. The oral administration of thyroid and the use of physical therapy were credited with aiding in the improvement. Further relapse has occurred since an attack of coronary thrombosis and unsatisfactory progress of litigation.

CASE OA230 (N. V.).—*Probable Early Generalized Scleroderma; Failure of Sympathectomy; Healing of Ulceration with Dibenzyline*

A 53-year-old woman was seen in the fall of 1951, complaining of recurrent painful fingers with ulceration of the finger tips of seven years' duration. Blanching and cyanosis had been noted on exposure to cold, but there were also times in all seasons when these color changes would be observed without known cause and would last for days or weeks. Cough had also been present, and x-ray showed extensive pulmonary fibrosis. A bilateral dorsal sympathectomy (T_2 and T_3) had been performed in 1946, without relief. Ulceration of the finger tips had been present quite steadily during the past year.

Examination of hands showed cold doughy swelling of the fingers, with some loss of skin creases. The radial pulses were of good quality. The nails were deformed, and the finger tips showed tiny puckered ulcerations (Fig. 3*A*). X-ray showed loss of the distal tufting of the terminal phalanges. Biopsy of a finger tip showed heavy collagen in the dermis and subcutaneous tissue, with lack of its usual organization. Some of the small vessels of the dermis showed endothelial proliferation.

Fig. 3 (Case OA230).—*A*, ulceration in patient with scleroderma. *B*, healing after treatment.

Twenty milligrams of Dibenzyline were given twice daily, with prompt lessening of pain and slow healing of the ulcers. By March, 1952, the patient felt well (Fig. 3*B*) and the drug was discontinued. Some blanching and pain recurred in the summer, requiring a six-weeks' course of Dibenzyline.

CASE 8D917 (C. B.).—*Remittent Necrotizing Acrocyanosis; Rapid Healing with Dibenzyline*

A 63-year-old man suffered from arteriosclerotic heart disease. Rheumatoid arthritis had been present for one and one-half years, severe enough to make the patient leave his work. Cortisone was given over a three-month period, with slight improvement of the joint symptoms but with the production of a glycosuria and congestive heart failure.

While the patient was still on cortisone and as the heart failure was developing the finger tips became cyanotic and tender. Examination showed cold cyanotic fingers, with several small ulcerations of the finger tips (Fig. 4). There was moderate loss of skin and wrinkling of the fingers. The feet were normal. All the major pulses were of good quality. The cortisone was discontinued. The fingers became comfortable, with disappearance of the cyanosis and healing of the ulcerations after one week of treatment with 80 mg. of Dibenzyline a day.

CASE 7C103 (E. G.)—*Remittent Necrotizing Acrocyanosis; Failure of Dibenzyline to Protect against new ulceration*

A 33-year-old woman had suffered from blanching, coldness, and recurrent ulceration of finger tips for one and one-half years, with irregularly timed periods of exacerbation and improvement. In September, 1951, she was given 10 mg. of Dibenzyline four times a day. The response was excellent as regards the pain and coldness. Nevertheless, she still noted blanching of the fingers when excited (as watching her dog engage in a fight with another dog). In November, 1951, while she was still under treatment, a small ulcer developed on one finger tip. The patient discontinued attendance at the clinic.

CASE 3B756 (G. G.).—*Occlusion of Subclavian Artery (by Intramural Hematoma?); Episodic Vasospasm; Relief with Dibenzyline*

A 24-year-old man received a severe contusion of the left upper chest in an auto accident in the fall of 1951. The pulses of the left upper limb disappeared during the 24 hours following the

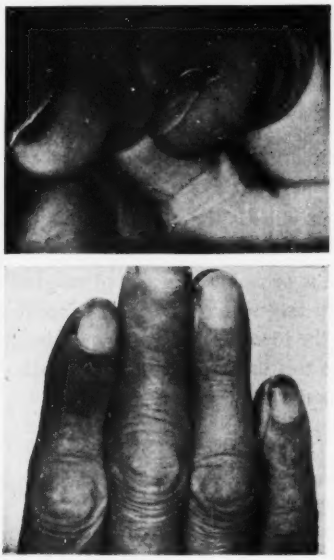

Fig. 4 (Case 8D917).—Digital necrosis and cyanosis in patient with remittent necrotizing acrocyanosis.

injury. The subclavian artery was explored by the scalenus route. It was patent but collapsed. The site of occlusion could be felt to be close to the aortic arch. Postoperatively the radial pulse was sometimes feebly felt. In the ensuing fall and winter months a distressing vasospasm appeared in the left hand on exposure to even slight cold. Sympathectomy was anticipated. The symptoms were, however, excellently controlled with 20 mg. of Dibenzyline, given four times a day for three weeks, then three times a day until late spring. By that time the collateral supply had apparently become adequate, for the radial pulse was now constantly of good volume. No further attacks of vasospasm appeared after the drug was discontinued.

CASE R9 (R. F.).—*Arteriosclerosis; Failure of Sympathectomy; Failure of Dibenzyline*

A 48-year-old man had diabetes, rheumatoid arthritis, and arteriosclerotic heart disease. Bilateral lumbar sympathectomy had been done for ischemic ulceration of both feet in 1949. The operation was considered technically correct, with removal of long segments of the trunks. Little response was obtained. Poor diabetic control and poor local hygiene allowed recurrent infection, necessitating a left low-thigh amputation in 1950.

Infection of the right fourth toe, in 1952, was accompanied by episodes of coldness and sweating of the foot and leg. No pulses were present below the femoral level. The sweating was easily controlled by 10 mg. of Dibenzyline, four times a day, but this did not bring with it any signs of increased blood flow. The drug was discontinued after one week. The toe was amputated and the wound successfully closed by a skin graft.

SUMMARY AND CONCLUSIONS

Dibenzyline (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride) has been given orally to 23 patients suffering from digital ischemia. Several patients were carried through two winters. Results were uniformly good in patients suffering from Raynaud's disease, the patients finding that they could go through the cold months with comfort. Dibenzyline failed to relieve the one patient suffering from minor causalgia.

The drug gave inconsistent results in patients suffering from disorders in which organic vascular occlusion predominates. It was, however, of value in relieving symptoms in two patients with occlusion of major arteries until collaterals could develop.

The drug was given to two patients with residual activity after sympathectomy. In one with scleroderma the drug gave considerable relief, but in the second, suffering from arteriosclerosis, it corrected only excessive sweating.

In our experience Dibenzyline is the most effective of the vasodilators currently in use.

The use of Dibenzyline is probably superior to surgical sympathectomy for most cases of digital ischemia in the upper extremities. Partly because of the disorders more frequently affecting the lower limbs, and partly because the operation is technically more satisfactory in this instance, Dibenzyline will probably not find as wide application for ischemia of the toes.

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CEREBRAL METABOLIC DISTURBANCES IN HYPOTHYROIDISM

Clinical and Electroencephalographic Studies of the Psychosis of Myxedema and Hypothyroidism

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HISTORICAL REVIEW

THAT THERE are a variety of psychological changes seen in persons with myxedema is common medical knowledge, but there has been little study of this interesting relationship in the light of modern psychological and physiological concepts. In his original monograph, Sir William Gull [1] mentioned languor and occasional flashes of irritability in two cases of myxedema. Curiously, when this paper was republished in 1904 in a collection of his writings,[2] it was included in the section headed "Diseases of the Nervous System," this being the region he believed to be most affected.

> Although I do not think the nervous centres have undergone any discoverable anatomical change, nor is there any evidence that the intellect is materially injured, I believe the nervous power is upon the whole lessened, and hence have arisen the changes in the temper, and the attacks which have been described to me.

In 1888 a special committee of the Clinical Society of London [3] tabulated and summarized all the 109 cases of myxedema reported until that time and collected the following psychological symptoms:

> Delusions: Present in 18, absent in 28 cases (of a total of 46 cases in which their presence or absence was mentioned)
>
> Hallucinations: Present in 16, absent in 27 (total of 43)
>
> Insanity: Present in 16, absent in 29 (total of 45)
>
> Agoraphobia: Present in 12, absent in 21 (total of 33)

Although tiredness, lassitude, and apathy are generally considered the classical symptoms of myxedema, these authors further commented on

> Temperament: Irritability is a marked feature, though in exceptional instances the reverse is stated. In some cases placidity alternates with occasional outbursts of fretfulness or irritability.
>
> Sleep: In a large proportion sleep is noted as good, but in many of these there is excessive somnolence, especially in the daytime. In about one-third of the cases wakefulness is recorded, and sleep is often disturbed by horrible dreams and sensations. It may be noted that drowsiness during the day is very common in myxedema in both good and bad sleepers.
>
> Insanity: It takes the form of acute or of chronic mania, dementia or melancholia, with a marked predominance of suspicion and self-accusation.
>
> Agoraphobia: In many cases its mere existence is noted, but in a few, details are given, which show that this condition was undoubtedly present in a marked degree (p. 30).

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Little of basic importance has been added to the clinical descriptions of these original investigators, but numerous cases of myxedema have been reported in which the psychic symptoms were a prominent part of the clinical picture and often preceded the overt, physical manifestations. Approximately 100 convincing cases of myxedema with psychosis have been described since the 1888 report.* More than two-thirds of them are patients with spontaneous myxedema, while the remainder represent cases of myxedema following thyroid surgery or the radiation therapy of hyperthyroidism.

No accurate estimates of the incidence of psychological disturbances in hypothyroidism and myxedema are available. Wagner von Jauregg,[35] basing his figure on the original report of the London Committee, stated that 15% of such patients had psychotic symptoms. The psychiatric disturbance usually described includes gross behavioural, mood, and thought-content changes which not only have little specificity but also have a labile and shifting quality. Thus the behaviour may range from excitement to languor, the mood from mania to severe depression, and the thought content from suspiciousness to paranoid delusions, which may include the presence of hallucinations. Beck has emphasized the presence of hallucinations in 26% of a series of 194 consecutive cases of milder hypothyroidism as well as frank myxedema. He characterizes them as consisting most commonly of "small animals, generally mice, sometimes rats, cats or dogs running on the floor," and observed that "sometimes these visual disturbances take on the form of illusions, thus patients may see pictures distorted and move on the wall."[32] There have also been a few case reports of myxedema or hypothyroidism associated with nonpsychotic symptoms, such as "neurotic depression"[31] and "anxiety neurosis." When adequately treated with thyroid, most of the myxedematous patients with neurotic or psychotic symptoms improved significantly or recovered completely, though this was not always the case. In some the psychosis persists despite treatment.†

There is frequent use of such terms as "confusion," "disorientation," "stupor," "mental slowing," "bradypsyche," "dementia," "stupidity," and "clouding of the sensorium" in descriptions of the mental status of myxedematous patients. However, in most reports the emphasis has been on the clinical description of the psychotic mood, behaviour, and thought content rather than on elucidating the common denominator and underlying basis of the disorder. There is still mention of specific reactions associated with myxedema and hypothyroidism,[33] though it is generally admitted that the psychotic reaction often does not conform with any uniform nosological entity, as Kraepelin had implied.[4]

Both Wagner von Jauregg[35] and Akelaitis,[22] however, stated that they believe that the psychosis is fundamentally of an "organic" type and that the psychosis is therefore symptomatic and individual, thus explaining its variability. On the basis of Rorschach testing of 15 myxedematous patients, Reitan[34] concludes that "Intellectual functions suffer some impairment with myxedema. The performance of myxedematous patients falls between that of neurotic patients and that of patients with organic brain damage."

In the light of modern concepts of delirium, first elucidated by Romano and Engel,[36] the psychosis of myxedema resembles that seen in many different disturb-

* References 4-33.

† References 20 and 22.

ances of cerebral metabolism, caused by a multiplicity of agents—anoxia, acute alcoholic intoxication, hypoglycemia,[37] and acute arsenical encephalopathy [39]—and may be seen in systemic diseases such as pernicious anemia,[40] cardiac and pulmonary failure,[42] Addison's disease, and uremia. If these metabolic disturbances do not lead to permanent damage of the nervous system, they give rise to the clinical picture of delirium characterized by a reversible impairment of the level of awareness. The most useful and sensitive single clinical test for delirium has been found to be serial subtraction of numbers; this is not intended to measure arithmetical ability but rather to test "attention, concentration, endurance and utilization of concepts without sensory guidance." [36] In severer delirium defects may be found, in addition, in any or all of the areas (orientation, memory, retention and recall, calculation, general knowledge, etc.) evaluated in the usual examination of the sensorium. It is, however, the sensorial disturbances that are basic and the behavioural, mood, and thought-content changes which are superimposed and represent a "release" phenomenon.

No completely satisfactory method for studying cerebral metabolism has yet been developed. However, such metabolic disturbances may be reflected by means of the electroencephalogram and, more directly, by the nitrous oxide method of Kety and Schmidt.[41]

Numerous studies have implied that electroencephalographic changes parallel changes in cerebral metabolism and that in delirium electroencephalographic alterations can be correlated with the clinical evaluation of the level of awareness.[42] In general, the electroencephalogram in mild delirium shows a shift to frequencies below the normal alpha range, which is considered to be from 8½ to 13 cps. However, in persons who normally have a basic rhythm which falls in the rapid range of the alpha spectrum, considerable slowing and clinical delirium may be present although the basic frequency remains above 8½ cps. With more marked delirium there is greater slowing of the mean countable frequency, accompanied by the appearance of intermittent low-voltage fast activity, which may occupy almost the entire record in some cases. In a severe derangement of cerebral metabolism the electroencephalogram consists largely of irregular, moderate to high voltage, 1 to 8 cps slow waves. By using a quantitative method of analysis of the EEG frequencies it is possible to correlate EEG and the level of awareness with considerable precision.[43]

Bertrand, Delay, and Guillain [44] reported on the electroencephalogram in four adult (acquired) cases of myxedema and three cretins and summarized their findings as follows: low voltage and rarity of waves, absence of alpha rhythm and presence of irregular 3 to 4 cps waves, no change with opening the eyes, and similarity of the tracing from all areas of the brain. The slowing and low voltage have been confirmed by subsequent investigators.[45] Ross and Schwab [46] reported good correlation of basal metabolic rate (BMR) with EEG frequency in 12 cases of myxedema but stated that the correlation was less satisfactory in hyperthyroidism. Other investigators [47] have also found EEG frequency and BMR to be relatable, and Rubin, Cohen, and Hoagland [48] reported that the EEG frequency in euthyroid schizophrenics could be increased slightly by giving large doses of thyroid but could not be maintained at greater than 13 cps (reached in one case).

More recently, García Austt ‡ has reported electroencephalographic studies on 57 patients suffering from primary adult myxedema and has compared them with the tracings obtained in cases of pituitary myxedema.[49] In the former he has found that during the development of myxedema the first change to be noted is a gradual decrease in frequency that rarely attains 7 cps and never goes below that limit. At the same time that the hypothyroidism increases, a reduction of voltage occurs to a point where no waves are visible.

In two cases of pituitary myxedema studied by the same author the frequency fell to levels of 3 to 6.5 cps, with coincident increase in voltage. The authors believe that the EEG changes in primary myxedema are the result of reduction of the respiratory rate of cerebral cells secondary to a fall in circulating thyroid hormone.

That the cerebral metabolism is indeed disturbed is indicated in the studies of Scheinberg, Stead, Brannon, and Warren.[50] Using the nitrous oxide technique, they have shown that in eight myxedematous patients the average cerebral blood flow was 38% below normal, oxygen and glucose consumption 27% below normal, and cerebral vascular resistance 91% above normal. Their data suggest a correlation between the disturbance in brain metabolism and mental status, in that all the patients showed symptoms of sensorial impairment and one was "frankly psychotic, with delusions and hallucinations." "Three patients who were restudied following thyroid therapy showed a definite return toward normal in all their cerebral metabolic functions," accompanied by "clinical improvement in appearance, general well-being, mental status, and basal metabolic rate." EEG's were recorded from five of the eight patients, and four of the five were found to show one or more of the characteristics originally delineated [44]; repeat EEG's of two patients after treatment with thyroid revealed increased frequency in one and increased voltage in both records. No attempt was made to correlate the EEG with the level of awareness.

We hope to show in this report that in certain of the "psychoses" with myxedema and hypothyroidism the clinical changes are due to a reversible impairment of cerebral metabolism, reflected by electroencephalography and mental-status examination.

METHODS AND MATERIALS

In the past three years, seven psychotic hypothyroid patients have been studied on the medical and psychiatric wards, as well as in the respective outpatient departments, of the Strong Memorial and Rochester Municipal Hospitals. Three of the patients (R. B.; B. M.; M. S.) were grossly myxedematous, and the remainder suffered hypothyroidism of various etiologies. In one case the illness followed treatment of thyroid with radioactive iodine (A. S.), and in the remaining three it apparently was spontaneous in origin. In all cases the predominant presenting symptomatology was of the psychosis and not of the hypothyroid state. The clinical diagnosis was confirmed by estimation of the serum-cholesterol level, basal metabolic rate, and radioactive iodine uptake and, whenever possible, a determination of the protein-bound iodine level. Mental status examinations and electroencephalography were carried out on admission and serially after the institution of thyroid therapy. All other causes of delirium were carefully ruled out by the appropriate clinical and laboratory techniques. Lumbar puncture was carried out in two cases (R. B.; L. M.). The clinical examination for delirium consisted of testing orientation, remote and recent memory, retention and recall, serial subtraction, and proverb interpretation. Past experience had taught us to pay especial attention to the level of awareness and to include observations of the speed, accuracy, and variation of response and of the patient's ability to

‡ García Austt, E., cited by Piaggio Blanco and co-workers.[49]

attend questioning and to persevere. Thus the manner in which the patient performed the serial subtraction of 3 or 7 from 100, as well as his arithmetical skill, was the best estimate of his level of awareness.

Electroencephalograms were recorded by the same technician on a six- and eight-channel machine (Grass Model III C No. 321) in the standard manner. From these records a quantitative frequency distribution and mean frequency were calculated by the method described by Engel and co-workers.[43] § The mean frequency was then correlated with changes in the mental status.

Under thyroid therapy, the clinical status and improvement were followed by various laboratory tests to confirm the disappearance of the symptoms.

RESULTS

All our seven patients were delirious by clinical criteria, but there was a marked variation in degree. Two patients (R. B.; M. S.) showed such patent fluctuations in behaviour, attention, and the level of awareness, as well as forgetfulness, that there could be no doubt as to the underlying disturbance. In the other patients,

TABLE 1.—*Data on Seven Hypothyroid Patients with Psychosis*

	Mental Status		Electroencephalogram, Waves/Second				
			Before Treatment		After Treatment		
Case	Before Treatment	After Treatment	Lowest Frequency	Mean Frequency	Lowest Frequency	Mean Frequency	Dosage
1	Manic; delirium gross	Mild depression, sensorium clear	6	7.2	8	11.6	Thyroid, U. S. P., 15 to 90 mg. for 6 mo.
2	Depressed; paranoid; delirium mild	Mild anxiety, sensorium clear	7	8.5	12	14.2	Thyroid, U. S. P., 45 to 120 mg. for 10 mo.
3	Depressed; paranoid; delirium	No abnormality, delirium mild	6	7.07	8	8.96	Thyroid, U. S. P., 60 to 120 mg. for 9 mo.
4	Anxiety; somatic delusions; delirium mild	No abnormality, sensorium clear	6	7.00	Low-voltage fast		Thyroid, U. S. P., 75 to 120 mg. for 7 mo.
5	Depressed; anxious; serial subtraction defect	No abnormality, sensorium clear	6	7.68	8	8.98	Thyroid, U. S. P., 15 to 90 mg. for 6 mo.
6	Depressed; agitated; delirium moderate	Mild gaiety, delirium mild	7	8.35	8	9.79	Thyroid, U. S. P., 15 to 180 mg. for 2 mo.
7	Depressed; paranoid; delirium moderate	No abnormality, delirium mild	7	8.52	8	9.17	Thyroid, U. S. P., 6 to 30 mg. for 3 wk.

however, the sensorial impairment was more subtle and could only be detected by formal testing. This was particularly true of one patient (A. S.), whose presenting complaints of severe mood depression and anxiety overshadowed her sensorial defect, that was characterized only by difficulty in serial subtraction.

In two cases also (R. B. and B. M.) there were such serious disturbances in behaviour, mood, and thought content that, had it not been for their grossly myxedematous appearance and our persistent testing of the sensorium, the diagnosis might have been overlooked.

In viewing Table 1 it also becomes apparent that although all seven patients were psychotic they failed to demonstrate any uniform behavioural characteristics. Three cases evidenced an admixture of depressive and paranoid features, two were depressed and markedly anxious, one showed an intensely manic reaction, and one suffered bizarre somatic delusions and persistent symptoms of anxiety reaction.

Two cases representative of the two extremes of clinical delirium follow.

CASE 1.—Mrs. R. B., a 55-year-old housewife, was admitted to the psychiatric ward of the Rochester Municipal Hospital in October, 1950. In the summer of 1949 she had been treated by

§ Dr. George L. Engel made the frequency counts.

a physician with thyroid extract to correct her obesity, with a coincident loss of 20 lb. (9 kg.). Photographs taken at that time reveal her myxedematous appearance.

In the year prior to admission, she had suffered occasional lapses of memory and became unexpectedly profane, self-assertive, and demanding. Two and a half weeks before hospital entry she had become fitfully uncontrolled in her anger; thereafter she was more and more expansive, irritable, uninhibited, jocular, and harried. Her speech flowed freely and rapidly to the point where she could no longer utter a word but instead wrote furiously.

On admission examination her vital signs were unremarkable. She was obese and had a wrinkled puffy face, and her enlarged tongue gave her speech a husky, thick, slurred quality. The skin was yellowish, dry, and pitted in all areas. Body hair was generally thinned out but was present in the axillae; it felt coarse to the touch. The rest of the examination was unremarkable except for sluggish deep tendon reflexes throughout.

Mental-status examination revealed a variably attentive, irritable, hyperactive, gay, infectiously humorous woman who spoke continuously and frequently rhymed and joked when not writing furiously. She was oriented in all spheres; her memory for recent events was defective, as was her ability to calculate, and she serially subtracted inaccurately and with marked variation in performance. Abstractions were literalized. Psychological testing confirmed the presence of an organic reaction.

The hemoglobin concentration was 13.1 gm. per 100 cc.; the white blood cell count was 6,400 per cubic millimeter. Urinalysis showed only a trace of albumin. Chest x-ray revealed a heart whose transverse diameter was at the upper limits of normal. Fasting blood sugar was 75 mg. per 100 cc.; serum cholesterol, 485 mg. per 100 cc.; serum sodium, 100 mEq. per liter, and serum potassium, 4.5 mEq. per liter. The basal metabolic rate averaged —41%; the uptake of a calculated dose of radioactive iodine was 4.8% in 24 hours; the electroencephalogram showed extremely low voltage and had a mean frequency of 7.2 cps (EEG III, Chart 1). The cerebrospinal fluid contained 50 mg. of protein per 100 cc. An electrocardiogram was interpreted as showing low voltage and prolonged "K."

During the first 13 hospital days the patient became increasingly delirious and her manic reaction lead to exhaustion. Following the administration of thyroid extract, U. S. P., ¼ grain (15 mg.), the patient became even more active, hallucinated, and violent and showed complete cloriding of her sensorium, as well as slowing of the frequency of her electroencephalogram. This episode was believed to have been caused by relative adrenal cortex insufficiency, as evidenced by a lack of eosinophiles following the administration of a test dose of epinephrine and corticotropin. After this her sensorial defect and EEG returned to their pretreatment levels. As thyroid medication was increased weekly by a ¼ of a grain (15 mg.), there was a gradual diminution of her psychotic behaviour. At the end of six weeks of treatment there was disorientation as to the exact date; she serially subtracted with but two errors, and the mean frequency of the electroencephalogram was now 8.5 cps (EEG X, Chart 1). At the time of discharge the patient was attentive, friendly, and controlled in speech and action and the sensorium was clear. The patient had amnesia for the period of her severest excitement. At this time EEG mean frequency was 9.4 cps. The patient was discharged on a dosage of 2 grains (120 mg.) of thyroid extract per day. Two and five months after discharge the electroencephalogram had stabilized at 11.5 cps; serum cholesterol level was 235 mg. per 100 cc., and the basal metabolic rate was —9%.

This patient demonstrated severe delirium, of variable nature, accompanied by a manic reaction, which cleared coincident with thyroid medication, accompanied by return of her electroencephalogram to normal.

The next patient had a much milder degree of delirium but manifested behavioural changes and had an electroencephalogram whose frequency fell within the accepted range of normal.

CASE 2.—Mrs. B. M., a 48-year-old housewife, was admitted to the medical wards of Strong Memorial Hospital in January, 1951, with at least a year's history of languor, unexplained crying spells, inability to concentrate or act rapidly, swelling of her tongue and legs, "numbness" and stiffness of her fingers, and dryness of her skin. She became unable to work, had doubts about her husband's fidelity, and was convinced that she had syphilis.

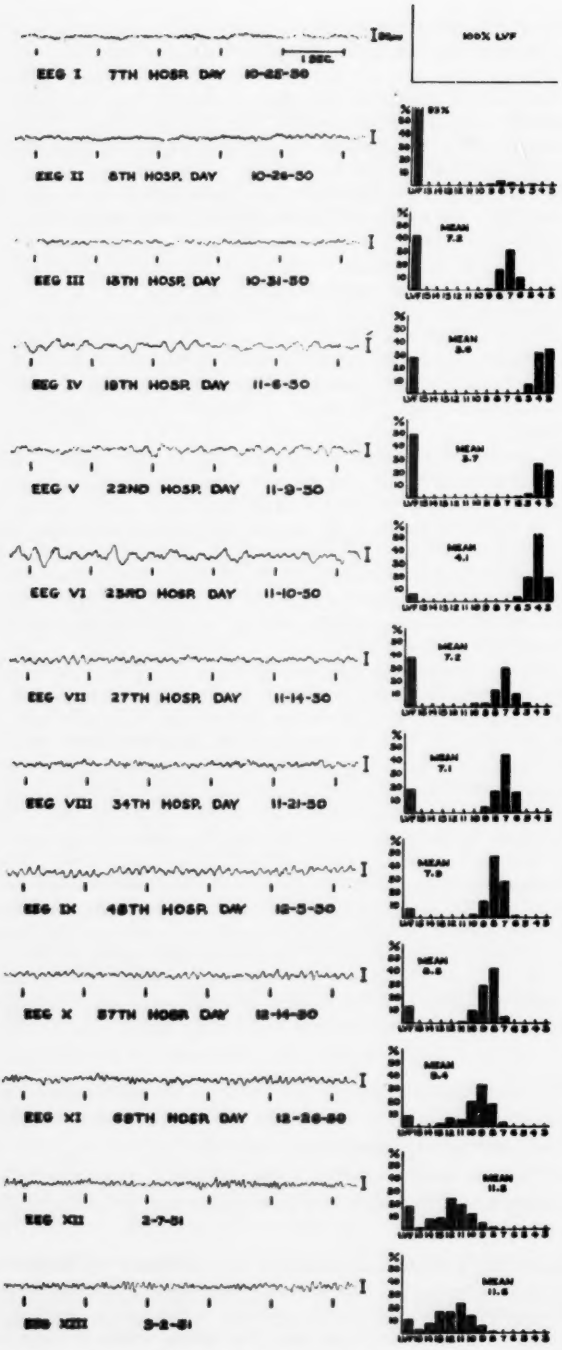


Chart 1 (Case 1).—Serial electroencephalograms of R. B., a 55-year-old woman.

On admission her appearance was characteristically myxedematous. No aberrations of the vital signs were obtained, and her general physical examination was otherwise unremarkable. The patient was irritable, hostile, anxious, and suspicious and was subjectively and objectively depressed; she criticized herself, stated that she felt inadequate, and was deluded about her husband's fidelity. Testing the sensorium revealed only a fluctuating disorientation and marked heightening of effort on incorrect serial subtraction. The hemoglobin concentration was 9.5 gm. per 100 cc.; the white blood cell count, 5,200 per cubic millimeter; the urine was normal; the serum cholesterol level was 395 mg. per 100 cc.; the radioactive iodine uptake, 4% in 24 hours; a basal metabolic rate could not be established; there was some degree of cardiac enlargement

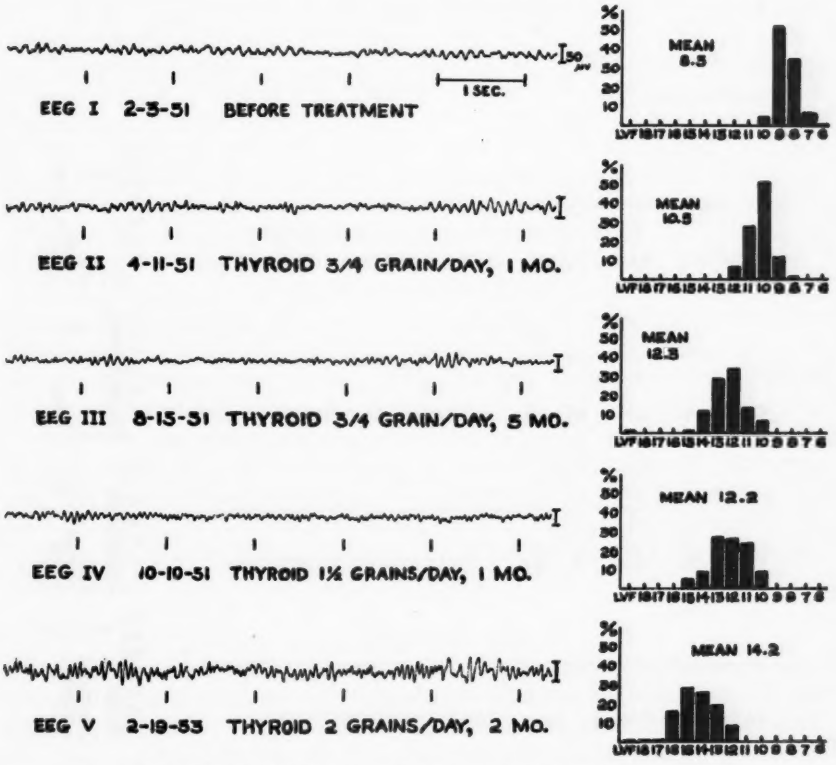

50 μv
1 SEC.
EEG I 2-3-51 BEFORE TREATMENT
MEAN 8.5
EEG II 4-11-51 THYROID 3/4 GRAIN/DAY, 1 MO.
MEAN 10.5
EEG III 8-15-51 THYROID 3/4 GRAIN/DAY, 5 MO.
MEAN 12.3
EEG IV 10-10-51 THYROID 1½ GRAINS/DAY, 1 MO.
MEAN 12.2
EEG V 2-19-53 THYROID 2 GRAINS/DAY, 2 MO.
MEAN 14.2

Chart 2 (Case 2).—Serial electroencephalograms of B. M., a 48-year-old woman.

by x-ray; an electrocardiogram revealed low voltage; the electroencephalogram also showed low voltage, having a mean frequency of 8.5 cps, with some 6 and 7 cps activity present.

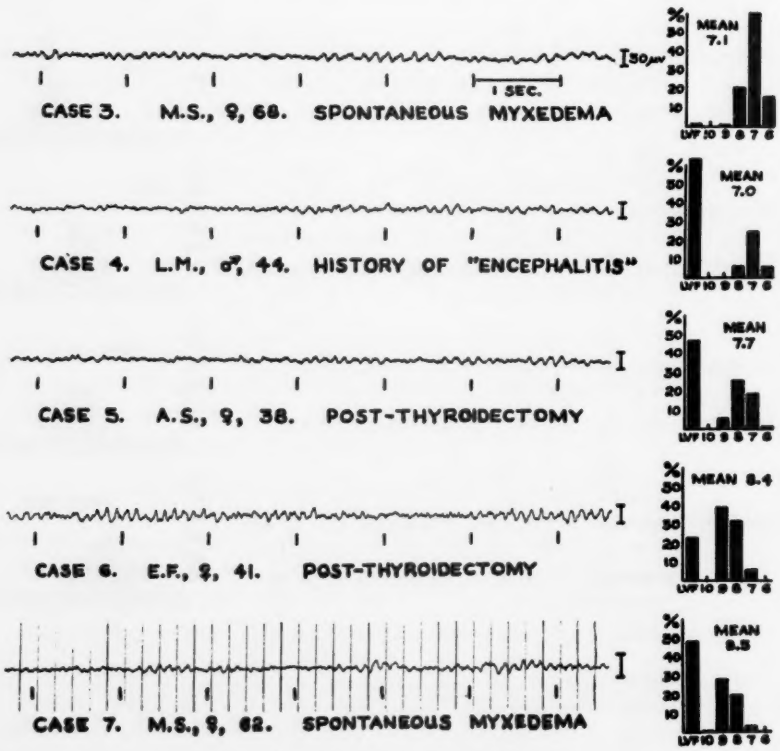
The initial dosage of thyroid extract was ¼ grain (15 mg.), which was increased by an equivalent dose every two weeks. After two months, while she was taking ¾ grain (45 mg.), there had been some improvement in her feeling of well-being and a greater ability to concentrate but she was still depressed and deluded about venereal disease. Sensorial testing revealed no aberrations except for some hesitation in serial subtraction and a mistake that was corrected by the patient. The electroencephalogram (EEG II, Chart 2) now showed an increase in voltage and a mean frequency of 10.5 cps.

Six months after the beginning of treatment, while she was still on ¾ grain (45 mg.) of thyroid extract, there was further improvement in her psychological condition and sensorial

TABLE 2.—*Results of Thyroid Treatment*

				Before Treatment				After Treatment	
Case	Patient	Age, Yr.	Sex	Serum Cholesterol, Mg./100 Cc.	I^{131} Uptake, %	BMR, %	Serum P. B. I., γ/100 Cc.*	Serum Cholesterol, Mg./100 Cc.	BMR, %
1	R. B.	55	F	485	4.8	−41	...	235	−9
2	B. M.	48	F	395	4.0	−22	...	260	+8
3	M. S.	68	F	500	2	−17	1	270	...
4	L. M.	44	M	420	...	−25	...	225	+13
5	A. S.	38	F	...	<10	− 8	1	...	...
6	E. F.	41	F	340	4.8	−17	...	176	−7
7	M. S.	62	F	619	3.2	−35	...	380	0

* Protein-bound iodine level.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CASE 3. M.S., ♀, 68. SPONTANEOUS MYXEDEMA
MEAN 7.1
CASE 4. L.M., ♂, 44. HISTORY OF "ENCEPHALITIS"
MEAN 7.0
CASE 5. A.S., ♀, 38. POST-THYROIDECTOMY
MEAN 7.7
CASE 6. E.F., ♀, 41. POST-THYROIDECTOMY
MEAN 8.4
CASE 7. M.S., ♀, 62. SPONTANEOUS MYXEDEMA
MEAN 8.5

Chart 3.—Pretreatment electroencephalograms.

performance and an increase of electroencephalographic frequency, to 12.2 cps. However, she still was not completely her former self; hence her thyroid dosage was gradually increased to 2 grains (120 mg.) daily over a period of one year. Not until she had been on the latter dose for three months did she become completely asymptomatic. All evidence of sensorial impairment had disappeared and her electroencephalogram had shown further increase in voltage, with a mean frequency of 14.2 cps. No evidence of overmedication was obtained.

Such a mild degree of delirium as this patient showed may easily go undetected, and the psychotic behaviour may be considered "functional." Furthermore, the electroencephalographic mean frequency might have been considered within the normal range, though at its low end.

As in several previous studies of delirium, irrespective of cause, there was good correlation with the electroencephalogram. The two most severely delirious patients (Cases 1 and 3) had the lowest mean frequencies, whereas those less affected in regard to their level of awareness had higher mean frequencies prior to treatment, with the exception of Case 4. Even when the frequency fell within the low normal range there was a significant increase with thyroid medication and coincident clearing of the sensorium (Cases 2 and 7).

All patients responded to thyroid medication in varying doses, and all, with one exception, have had complete or partial clearing of the sensorium and progressive increase of mean frequency of EEG waves, although it is believed that only in Cases 1 and 2 has stabilization occurred. Four of the delirious patients now have no sensorial defects, while three have responded partially by clearing on what we believe has been suboptimal dosage, or else there has been insufficient time for follow-up. In all cases the psychotic behaviour accompanying the delirium has disappeared.

During treatment with thyroid extract two of our patients complained of the anxiety reaction which is often said to be a symptom of overdosage. However, the anxiety reaction is also a frequent accompaniment of delirium, irrespective of cause, and in both patients, who were still mildly delirious, it disappeared with upward adjustment of the dose.

The electroencephalograms obtained in these patients all have strikingly similar appearances and resemble those obtained by other authors (Chart 3). Except for one case, the improvement noted has been a progressive increase in voltage and mean frequency. We have reason to believe, however, that such improvement is slow in stabilizing, even on an optimal dose, as those patients who have had the longest follow-up have shown the maximum improvement.

COMMENT

These seven psychotic hypothyroid adults all showed clinical delirium. Whereas in other forms of delirium the electroencephalographic waves increase as their frequency decreases,[42] in hypothyroidism and myxedema there is both slowing and lowering of voltage. Despite this, the evidence, both clinical and by the nitrous oxide technique, is that these electroencephalographic changes are due to an impaired state of cerebral metabolism.[50] We have considered that the lowering of voltage that is a prominent accompanying feature of the electroencephalogram might be due to an increase of the skin resistance in myxedema; however, on theoretical grounds this is not considered possible.|| If there is a specific physiological disturbance affecting the central nervous system of these patients that explains this variation, it remains unidentified.

In all cases, with therapy there has been clearing of the delirium and electroencephalographic improvement, indicating that when thyroid medication is admin-

|| Grass, A. M.: Personal communication to the authors.

istered the cerebral metabolic defect is reversed. It is this defect which underlies the psychotic manifestations of the patient, which are, however, individual and do not fall into any uniform, classifiable category. This would explain the great variety of clinical pictures that have been described.

In all cases of delirium due to cerebral metabolic disturbances previously studied, the basic and uniform psychological defect is a disturbance of the level of consciousness, that may range from a mild serial subtraction and abstraction defect to stupor. The particular disturbances of mood, thought content, and overt behaviour in the delirious patient vary greatly and do not correlate with the electroencephalogram. They are individualized and are more understandable in terms of the preceding life experiences and psychological development of that patient than in terms of the underlying metabolic disturbance. It became evident on closer study of these patients that even in the euthyroid state they suffered from psychological maladjustment. In the delirious state, however, such problems are "released" and become much more manifest, giving a psychotic picture. Their nature is uninfluenced by thyroid therapy, though their gross manifestations disappear as cerebral metabolism improves.¶ In our series, at least, all patients lost their psychotic symptoms, though others # have reported their persistence despite treatment; presumably in their cases an intercurrent or coincident psychosis had its onset with hypothyroidism.

It must be underlined that therapy only affects the impaired state of cerebral metabolism as reflected by the level of awareness, electroencephalogram, and the behavioural changes subsequent to such impairment. However, we believe that, in contradistinction to other reports, the psychosis of myxedema is fundamentally a delirium and not a specific and separate entity such as are the "functional" psychoses. In hypothyroidism we have been struck by the fact that most of the psychological symptoms disappear only when the sensorium has cleared and the electroencephalogram has become stabilized. This suggests that the latter may be used as an ancillary gauge of optimal therapy, although there remains a need to study nonpsychotic adult myxedematous and hypothyroid patients by these techniques.

SUMMARY

Seven psychotic adult myxedematous patients had varying evidence of a sensorial impairment justifying the diagnosis of delirium. This was considered to be due to a disturbance of cerebral metabolism and was accompanied in each case by characteristic electroencephalographic changes.

The delirium may be very mild in hypothyroid patients and may be the only clinical manifestation of hypothyroidism.

By the use of serial mental-status examinations and electroencephalograms during specific therapy, the status of the underlying metabolic defect can be followed.

The electroencephalogram may be used in following thyroid therapy, and return to normal levels roughly follows improvement of the delirium.

The psychosis of myxedema is not a specific reaction but is basically a delirium and, as in cases of delirium of other causes, follows no special behavioural pattern.

¶ References 36 and 40.

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Progress in Internal Medicine

OBESITY

Its Complications and Sequelae

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OBESITY is the commonest physical abnormality in the United States. Its incidence has been estimated to be one-fifth of the population. Furthermore, the incidence has been gradually on the rise to the point where the United States may have the dubious honor of being entitled the most overfed nation in the world. What are the penalties of obesity? By the layman it is recognized as a definite esthetic, social, and economic handicap. To the physician the obese person is the victim of a disease accompanied by a high incidence of certain associated physical and mental pathological states and a decidedly decreased longevity. Keys [1] has pointed out the astounding fact that this country, which has the best medical care in the world, has the highest mortality rate in the middle-aged populations. In the 16 countries which have reliable vital statistics only the population of Portugal and the women of South Africa had a higher death rate than the United States. The greatest problems facing medicine today are the degenerative diseases of the middle and later years of life, and of these certainly obesity is one of the foremost. The purpose of this paper is to emphasize the complications and sequelae of obesity. The light vein in which many physicians prescribe weight reduction and the ease with which they themselves fall victims of the disease suggest that the consequences of obesity are not fully appreciated. Many of the valuable data on the effect of obesity on longevity have been assembled by various actuarial groups, who have understandable interest in the subject. These data are not generally available to the physician. Thus a comprehensive review is presented which covers this valuable material as well as the general medical literature.

Obesity has its genesis from the Latin word *obesus,* which is the past participle of *obedere. Obesus* would best be translated as "that which has eaten itself fat." Obesity has been defined by Epstein [2] as an increase in body weight in excess of the limitation of skeletal and physiological requirement, due to the deposition of fat. The height-weight charts found in standard texts of nutrition are usually derived from the 1912 medicoactuarial standards but have been modified in some slight detail by many authors. Clinically this type of table usually suffices to segregate the overweight. In general throughout the literature, 10% above the standard weight has been considered overweight and 20% above the standard weight has been considered pathological obesity. Such normal weight standards do have limitations, especially in the older age groups, as was pointed out by Brozek and Keys.[3] Using the more exact but cumbersome methods of estimating the amount of fat by measuring the

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skin folds and securing the body specific gravity by weighing under water, they found that the amount of fat in men aged 45 to 55 was strikingly greater. With age, they speculated that there is probably some replacement of muscle and other active tissues by fat, as well as the additional accumulation of fat. Thus the elderly men who are rated as having "normal" weight by actuarial standards might actually have considerable excess fat depots. Other methods that have been found to correlate with obesity are thoracic and/or abdominal girth measurements. These offer a compromise in accuracy between the height-weight tables and the underwater weighing.

ETIOLOGY

Although the primary purpose of this discussion is to review the literature regarding the sequelae and complications of obesity, it might not be amiss to review briefly some of the current concepts regarding the etiology of obesity. This knowledge is a prerequisite to any speculation on the nature of the relationship between obesity and the diseases which are frequently associated with it.

First there is the question of heredity. It is generally conceded that obesity is significantly more frequent in the parents of the obese patients than in those of a control group of subjects of normal weight. This fact has been well documented by Gurney.[4] In his study of the progeny of different parents, he concluded that segregation of obese progeny with obese parents was suggested and listed this as evidence for the Mendelian inheritance of build. Bleisch and his co-workers [5] demonstrated in a certain strain of mice an obesity which was inherited as a simple Mendelian recessive and had associated diabetes mellitus and insulin resistance. However, most of the workers in the field of obesity are inclined to disavow any hereditary factor in human obesity. They attribute the familial incidence to conditioning and family custom. It is certain that the majority of the obese who have this familial trend respond to dietary therapy as well as any other group. Two rare syndromes which include the symptoms of obesity in which Mendelian inheritance has been demonstrated are the Laurence-Moon-Biedl syndrome (as recessive) and the Morgagni-Stewart-Morel syndrome (as dominant).[6]

There is some evidence that there is neurogenic control of appetite. Frazier,[7] in reviewing 105 cases of proved cerebral neoplasms limited to the frontal lobe, listed hunger as one of the symptoms. It has long been known that the development of obesity occurs in animals after destructive lesions in (or ventrolateral to) the ventromedial nucleus of the hypothalamus. This obesity results from hyperphagia. A review of the hypothalamic obesity is given by Brobeck.[8] This type of obesity is sometimes found in man, due primarily to a neoplastic or infectious process in the region of the diencephalon or its neighbor, the hypophysis. It should be suspected in human obesity which begins abruptly and whose onset coincides with other signs and symptoms of a disease process at the base of the brain. More recently, Anand and Brobeck [9] have demonstrated a well-localized lesion in the lateral hypothalamus of the rat which is followed by a complete absence of eating. This effect was observed also in animals in whom "hypothalamic obesity" had first been produced.

Psychological factors often play both a cause and an effect role in obesity. Hamburger [10] has stressed the high incidence of associated psychological abnormalities in the obese. He has given examples demonstrating obesity that have been largely psychogenic in nature in response to nonspecific emotional tensions, as a substitute for gratification in intolerable life situations, and as a symptom of underlying emo-

tional illnesses, especially hysteria and depression. Hamburger also has noted some people with a compulsive craving for food, which he suggested was a food addiction. There can be no doubt that overeating often subserves strong emotional need. These abnormal psychological patterns may become fixed in childhood and the obesity manifest itself early. Often it can be predicted from the behavior pattern of the mother, which is characteristically overprotective in nature. The obese are "set apart," often deprived of marriage and other social and physical activities of their peers. This creates new conflicts and tends to perpetuate the neurosis and the obesity.

For years it was the custom among many physicians to ascribe obesity to "the glands" and treat it with some gland extract. Most authorities now agree with Rynearson [11] that "endocrine disorders are rarely if ever a cause of pronounced obesity." It has been correctly cited that corticotropin (ACTH) and cortisone administration produces increased appetite. Cushing's syndrome, however, is not invariably associated with overweight. Panhypopituitarism will usually have little effect on body weight. The terms "Frohlich's syndrome" and "adiposogenital dystrophy" have been used much too freely. Rynearson [11] states that there is no convincing evidence of endocrine or central nervous system involvement in many cases previously so classified. He suggests that these terms be restricted to obese sexually immature males who have passed the normal age of puberty and in whom there is additional evidence of a lesion involving the region of the hypothalamus and hypothysis. There is no evidence that hypothyroidism causes obesity. Islet-cell tumors of the pancreas sometimes result in obesity as a result of the hunger produced by the hypoglycemia. In this regard Mayer and Bates,[12] studying the levels of various metabolites in rats, dogs, and mice, found that food intake was strikingly correlated with variations of the blood glucose but not with those of other metabolites directly. However, in man obesity is not frequently seen in functional hypoglycemia, and hypoglycemia is rarely observed in the obese. One must conclude that in humans there is no substantial evidence that blood glucose or any other metabolite serves as a chemoreceptor regulating the food intake.

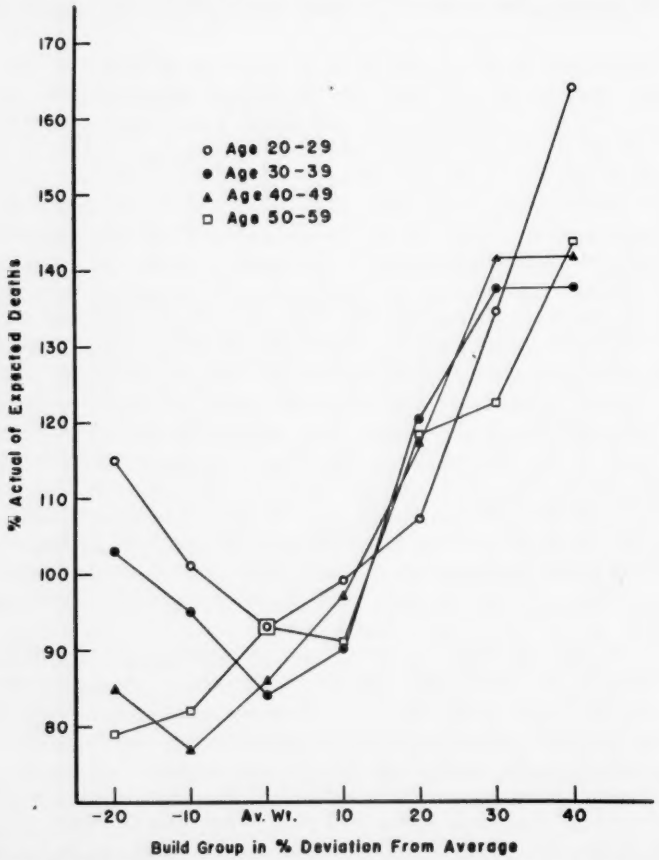
Rynearson and Gastineau [6] have reviewed the literature and accumulated convincing evidence against the many theories of disorders of the use of energy proposed as having a role in the production of obesity. Examples of these discarded theories are excessive gastrointestinal absorption, "static" obesity, increased efficiency in doing work, and reduced specific dynamic action.

Demonstrable pathology that bears a causal relationship to obesity is rare. Thus one is left with the realization that at least 95% of the cases of obesity are probably due to unadulterated overeating or "gluttony," as was implied by its Latin derivation. As Rynearson * often emphasizes, "Fat comes only from food, and obesity results only from eating more than is required to meet the energy requirements of the body. The one treatment of obesity is diet." Thus the pathological mechanism involved seems to be an increased appetite, but further research is needed to determine whether its nature is primarily psychological, neurogenic, or chemical. Calorically speaking, inactivity plays a minor or secondary role. Brooks [13] likewise reached this conclusion when he measured the activity of rats with hypothalamic obesity. Clinically it is rarely possible to effect reduction by exercise without restricting the caloric intake.

* References 6 and 11.

CORRELATION OF OBESITY AND MORTALITY

For over two decades the unrelenting efforts of actuarial groups, principally that of Dublin, of Metropolitan Life Insurance Company, have been primarily responsible for making the physician and the public aware of the influence of obesity on longevity. In 1932 the Actuarial Society of America published the collective data [14] of 32 life-insurance companies on the correlation of obesity with mortality in males.



Effect of weight on mortality of insured men, standard and substandard issues combined, by ages at issue; experience from 1909 to 1928.[14] The class end-points of the two extreme weight groups are only approximate.

This study included all standard and substandard policies combined between 1909 and 1928. The data were tabulated by the age and weight at the time the insurance was issued.

This study showed rather conclusively that in general the overweight men had mortality well above the average; the greater the overweight, the greater the mortality. Subsequent similar long-term actuarial studies † have revealed similar

† References 15-18.

results. One weak point in the actuarial studies is that the patients were not followed and it is not known that they maintained their obesity. From the natural history of obesity one can be relatively certain that most of them did. The high mortality shown in the lower-age underweight groups is primarily the result of tuberculosis. Current studies do not show the trend.

A review of the medical histories of 3,343 clerical workers of the Metropolitan Life Insurance Company from 1930-1943 [19] and a review of the records of 5,021 Army officers [20] reveal a similar trend. Both these groups had periodic physical examinations. Starr,[21] measuring abdominal girth as an index of obesity, likewise found a uniformly increasing mortality rate with the degree of obesity. Experimental evidence also may be found to support the observation that overweight is correlated with a decrease in longevity. McCoy and his co-workers [22] demonstrated that rats kept underweight by restriction of calories outlive those allowed to fatten.

The first comprehensive study of actuarial data correlating build and mortality in females was published by Dublin and Marks [23] in 1939, and a follow-up study was published in 1951.[16] The mortality of overweight women, especially among the obese, was generally above average, although the figures do not show a significant progression of mortality with increasing percentage of overweight. The trend, however, is apparent. It was also noted that the obese females showed no trend in mortality according to age at the issue of the policy. This all seems to suggest that overweight is relatively better tolerated in women than in men as regards effect on longevity.

Dublin [16] recently published a study that covered 25 years and included 25,998 males and 24,901 females. In the obese the mortality in aggregate was 150% of the expected in males and 147% in females. What causes this decrease in longevity among the obese? The actuarial data discussed above list degenerative cardiovascular diseases, hypertension, diabetes, gall-bladder disease, and cirrhosis of the liver as leading causes of death in the obese. These and other conditions will be discussed individually in order that one may get some insight into the reason these diseases are correlated with obesity.

Degenerative Cardiovascular Disease.—For centuries it has been known that cardiovascular disease and "hardening of the arteries" are prevalent among the obese. Hippocrates noted that grossly overfed people often suffer a sudden death. Actuarial data and vital statistics uniformly place degenerative cardiovascular disease as the top cause of death in the United States.

Does overweight influence the mortality of degenerative cardiovascular disease? In Dublin's study [16] it accounted for approximately 50% of the total deaths in the obese, an incidence of 149% of the expected. Reed,[20] in reviewing the records of 5,021 Army officers, found that degenerative cardiovascular disease caused five times the death or disability of officers as did military combat during the period 1901-1929 (which included the Philippine Insurrection and World War I). In a more recent study, by Levy and his co-workers,[24] which reviewed the medical records of 22,741 Army officers, there was an observed increase in the number of retirements among the obese from this cause which was approximately one and one-half times the expected. Short,[25] in studying the electrocardiograms of 1,000 men receiving periodic health examinations, found that 45% of those 25% overweight or more had abnormal records. This was compared with 8.5% abnormality

in those of normal weight and 2% in those underweight. Simonson and Keys [26] found 13 out of 48 measured electrocardiographic items which showed statistically highly significant differences between lean and fat men. Further, they found that not all of these could be explained by the increased tendency for the horizontal electrical heart position and that the influence of body weight was more prominent in the older age groups.

In women, also, degenerative cardiovascular disease is significantly higher in the obese.‡ Dublin and Marks [23] found that the obese women had a mortality that was 50% higher than that expected for cardiovascular-renal diseases. At this point it may be worth while to recall the differences of sex incidence of arteriosclerosis. According to Durant,[27] the incidence is 24 times as common in the male in the 20's and 3.5 times as common in the 50's, and the sex incidence is equally divided in the 70's. Degenerative cardiovascular disease is exceedingly rare in the female before menopause, but the incidence rises steadily thereafter.

Additional support to the thesis that overweight causes increased mortality from arteriosclerotic heart disease is found in reports from countries that suffered deprivation of food during the recent war. There was a diminution in the number of cardiac infarctions and coronary diseases among the starving population during the seige of Leningrad.[28] A similar decline in degenerative heart disease was noted during the "lean" years of the war in Finland, Norway, and Sweden.§ In these countries, when the food supply returned to normal again, the incidence of these diseases again increased.

The published studies of the relationship of obesity to coronary aretriosclerosis in young men have been very interesting. French and Dock [31] studied 80 fatal cases of coronary thrombosis in young soldiers (age 20 to 36) and found that 73 were overweight and only 2 were thin, using the height-weight tables for determining the ideal weight. Yater and co-workers [32] studied 850 cases of coronary artery disease in men 18 to 39 years of age. They found no significant difference when the weights of their patients were compared with the weights in 297 cases of accidental deaths, in persons of similar ages. When compared with all inductees, they were a significantly heavier group. The difference was not significant when they were compared with men who had been in the Army for some time. In this group the proportion of markedly overweight men was about 60% greater among the survivors than among those who died. Garn and co-workers [33] studied 97 men who had had myocardial infarctions prior to the age of 40 and who were again active. They used as a control group healthy employed men of similar social and economic status. The weights in the two groups were similar, but in both it was higher than normal standards for all age levels. These studies merely serve to substantiate the impression that the average young adult male in the United States is now overweight when compared with the 1912 medicoactuarial standards.

However, does this overweight explain the higher incidence of degenerative cardiovascular disease in the United States? It is apparent that nonobese persons may be the victims of arteriosclerosis and, further, that not all of the obese have marked arteriosclerotic changes. In fact, in Yater's study [32] it would appear that the markedly obese had the better prognosis. A similar conclusion may be drawn

‡ References 16 and 23.

§ References 29 and 30.

from the study of the prognosis of angina pectoris by Dry and co-workers [34] at the Mayo Clinic. This study included observations on 6,882 patients with angina pectoris who had a 5 to 10 year follow-up. The 5-year survival for the entire series was 58.4%, and the 10-year survival was 37.1%. In 377 obese patients with angina pectoris that were traced for 5 years and 250 that were traced for 10 years the 5-year survival was 70.0% and the 10-year survival was 44.4%. It would be interesting to know what percent of these obese patients lost weight and, further, whether there was modification in the carbohydrate-protein-fat ratio in the diet. Certainly the severe pain of angina and the sensation of impending death are strong incentives for reduction of weight. All clinicians have observed dramatic improvement in the obese angina patient with loss of weight.

Certain pathological studies also have attempted to define the relationship between obesity and arteriosclerosis. Wilens [35] studied 1,250 aortas at necropsy and correlated the weight of the patient with the degree of arteriosclerosis. He found the degree of sclerosis in the obese was greater than in the normal weight group and also that the sclerosis in the emaciated was less. In a subsequent publication [36] he inferred that premortem emaciation is followed by a decrease in sclerosis of the aorta. This conclusion was the result of the observation that severe or even moderate sclerosis is rarely observed in those who have suffered protracted undernutrition as a result of some wasting disease. Faber and Lund [37] studied the dry weight of the aorta and its cholesterol and calcium content in relation to the total body weight. They found that hypertension increased the weight of the aorta but that no specific effect was demonstrable in the obese normotensive persons. The same results were demonstrated in measuring the amount of cholesterol in the aorta. The amount of calcium in the aorta was more related to age; no specific effect could be attributed to obesity or hypertension.

In general we must conclude that obesity is highly correlated with degenerative cardiovascular disease. However, it is likewise as conclusive that obesity is not the sole factor involved. We must question whether this relation of obesity to arteriosclerosis is causal or the result of a common cause. Are they both the result of a common metabolic disturbance? Is the relationship only in that obesity is an index of overeating and that in overeating the subject consumes excessive amounts of certain constituents (e. g., fats and/or cholesterol) that predispose to arteriosclerosis? The theories of the pathogenesis of arteriosclerosis involve a tremendous field of research. Gofman [38] has attracted much attention in recent years by his investigations of the "giant molecules" of serum lipoprotein. He found these to have a higher relationship with arteriosclerosis than the serum cholesterol. He also observed that the two incriminated classes of lipoprotein molecules are significantly related to obesity.[39] Keys [40] indicated that some of the conclusions of Gofman and co-workers are to be criticized on the basis of statistical analysis. In another publication [41] Keys reviewed the "overwhelming" evidence of the relationship between arteriosclerosis and the concentration of cholesterol in the serum. His studies [41] on humans demonstrated that the serum cholesterol is independent of large differences in habitual cholesterol intake but fat seems to have great importance. In his studies of the population in Minneapolis, England, Spain, and Italy,[1] he has correlated the degree of elevated cholesterol and the mortality from degenerative cardiovascular disease with the amount of dietary fat intake. In the countries studied he stated

that "obesity is not the major factor in determining the serum cholesterol except in severe chronic undernutrition."

As previously mentioned, Durant,[27] using actuarial data, has called attention to the increased incidence of arteriosclerosis among the young ages. He also demonstrated that from 1910-1948 the caloric intake did not change appreciably in the United States but that there was a very definite increase in the calories derived from fat as compared with carbohydrate. He also noted that after the age of 40 obesity was a much commoner accompaniment of coronary disease. Malmros [29] attributes the decline of degenerative cardiovascular disease in Norway, Sweden, and Finland during the war to a decrease of food rich in cholesterol, although the total fat intake decreased too. However, he stated that in Denmark, where the total fat consumption declined but the consumption of butter and eggs increased, no fall was noted in the death rate during the war. Strøm and Jensen [30] state that total fat intake, including those foods rich in cholesterol, fell in Norway during the war from 159 to 71 gm. a day.

Thus the case incriminating obesity per se in cardiovascular disease is far from conclusive. The nature of the relationship will, undoubtedly, be forthcoming, but the subject requires much more investigation.

Hypertension.—Obesity has long been known to correlate highly with hypertension, and, indeed, weight reduction has played an important role in the treatment of hypertension. Master, Dublin, and Marks,[42] in a study based on random sampling (total sample of 15,706, of approximately equal sex distribution) among 74,000 industrial workers at every age and in both sexes, showed a steady progression in average blood pressure with body weight. Thomson [19] reviewed the records of 3,343 clerical employees, consisting of approximately an equal number of males and females, who had had yearly examinations in 1930-1943. He found a significant increase in the incidence of elevated diastolic pressure as the ponderal index (weight in pounds divided by the height in inches) increases, especially in the older ages. Between the ages of 45 and 54 the incidence of elevated diastolic pressure was 44.7% among the heavy, 33.4% among the medium, 28.4% among the medium light, and only 20% among the light. Levy and co-workers,[24] in reviewing the medical records of 22,741 Army officers, found that sustained hypertension developed in those overweight at a rate 2.5 times as high as in those in the control group. Green and Beckman,[46] in reporting a study of 1,260 obese patients, found that 11.8% showed hypertension when first examined. An additional 13.4% were normotensive when first examined but developed hypertension in a few years. Robinson and Brucer [44] used the chest-height ratio (which correlates well with obesity) for a comparison of body build with hypertension. They used an unselected series of 3,658 records of approximately equal numbers of each sex from the Life Extension Examiners in Chicago. In both males and females the mean systolic and diastolic pressures increase with the increase in the chest-height ratio. The lateral, or broad-chested, males have more than four times the expectancy of developing systolic hypertension and seven times the expectancy of developing diastolic hypertension as have men of linear, or slender, build. In the female those of lateral build have 11 times the expectancy for systolic hypertension and 8 times the expectancy for diastolic hypertension as do the linear-built females. In a subsequent publication [45] Robinson pointed out that the tall lateral, or broad, persons are more

susceptible to hypertension than the short lateral persons and are less likely to have low blood pressure. However, the lateral builds are commoner among short persons, thus causing the bulk of the hypertensive population to be found among the short persons.

Do the obese hypertensives have a worse prognosis? A publication by Ross [43] would seem to indicate that they do. He followed 88 persons with hypertension for an average of 32 months. Sixty-eight percent of his patients were overweight. The obese group had a higher incidence of coronary disease and left ventricular hypertrophy, higher average blood pressure, earlier average age, more elevated cholesterol level, more frequent and more serious retinal vessel changes, and a higher death rate from associated complications than did those who were of normal weight or underweight.

What effect does weight reduction have on the blood pressure? In Green's series [46] 71 of the obese hypertensives underwent weight reduction. Fifty percent of these had a drop to the normotensive level, with an average loss of weight of 13.9%. Ross [43] followed the effect of weight loss in 19 obese patients over a period of 200 months. No effect was observed in 12 patients; minimal lowering, in 5 patients, and moderate lowering, in 2 patients. Even with the small percent helped (approximately 40%) he found that weight loss surpasses other therapy in his armamentarium. It is interesting that in Leningrad [28] and Holland [47] during the periods of hunger in the last war a distinct fall in both the systolic and the diastolic pressure was observed. When the food supply returned to normal, the blood pressure rose in hypotensive, normotensive, and hypertensive persons. The severity of the hypertension was also increased, as measured by retinal changes. Brozek, Chapman, and Keys [48] observed a mean decline of 11.1% systolic and 7.73% diastolic pressure in men who were subjected to drastic food restriction (less than 1,600 Cal. a day) for six months. These men had no restriction of sodium intake. This study demonstrates conclusively that normotensive as well as hypertensive persons will sustain a fall in blood pressure on weight reduction, even when sodium is not restricted. When these men underwent dietary rehabilitation, their blood pressure returned to or slightly above the control level.

The role of obesity in hypertension is not at all clear. Green and Beckman,[46] in discussing this aspect, speculated on the factors in obesity that may be in part responsible for increasing the load on the heart: (*a*) The accumulation of fat around the heart and in the myocardium may make cardiac work more difficult, and at times may produce myocardial atrophy, due to penetration into the muscular wall; (*b*) an unduly elevated diaphragm due to the increased intra-abdominal fat content might cause a decreased negative intrathoracic pressure, which may increase the difficulties the heart has to meet, and (*c*) fatty tissue is rich in its vascular component, so that blood must travel a greater distance and frequently overcome increased peripheral resistance. One might question the validity of any one of these assumptions on a physiological basis. The work of Taylor, Brozek, and Keys [49] on basal cardiac function in the obese would seem to contradict the third assumption listed above. Using the acetylene method of determining cardiac output, they found that the largest cardiac output per square meter of surface area and per cubic centimeter of oxygen consumption will be found in muscular (large lean body mass) persons who have a small fat content. They found that fatness per se does not necessarily mean that basal cardiac output and cardiac work have been increased

in proportion to the increase in surface area or oxygen consumption. In view of the various neuroses reported to precede, accompany, and result from obesity, one might suspect that in some cases the psychological factors may be the common etiologic mechanisms. We know that factors other than obesity play a role in hypertension, and the effects of weight reduction in hypertension are inconstant. However, it seems certain that obesity is at least an aggravating factor in hypertension.

Diabetes.—The United States is said to have a higher percent of diabetes than any other nation.[50] This also is very probably the product of being the best-fed nation. Actuarial studies have long rated diabetes as one of the major causes of mortality among the obese. Recent long-term studies by Dublin and Marks [16] found diabetes to be four times the expected in the obese male and three and three-fourths times the expected in the obese female. Joslin,[51] in analyzing data from 1,000 successive cases of diabetes, found that of this series 77% were overweight, 15% were standard weight, and 8% were underweight at or preceding the onset of the disease. It must be recalled that loss of weight is a symptom of uncontrolled diabetes and is often present when the person is first seen by the physician. Further, obesity rarely accompanies the juvenile type of diabetes, but, beginning in the early 20's, obesity is present in the majority of those in whom the disease develops. To the obese diabetic weight reduction is just as important as insulin, or perhaps more so. In fact, Duncan [52] has stressed the inadvisability of treating the obese diabetic with insulin except during acute complications. Newburgh [53] found that in the mildly obese diabetics the glucose-tolerance test reverted to normal in 77% of the patients who cooperated fully with weight reduction. Malros [29] observed a decline in the diabetic morbidity and mortality in Sweden during the "lean" years of World War I. Allen [54] demonstrated as long ago as 1913 that partially depancreatized animals which were left enough gland to avoid diabetes became diabetic when they were overfed and became fat. Further experimental evidence of the diabetogenic nature of obesity is presented by Long,‖ who demonstrated that animals of a genus usually characterized by a good reserve of pancreatic function frequently developed typical diabetes when "hypothalamic obesity" was produced. Animals already diabetic suffered a pronounced exacerbation of the diabetes when the hypothalamic obesity was produced. In the obese there appears to be a chronic increased demand for insulin which might eventually be expected to overtax the capacity of the pancreatic islets and thus bring on diabetes. Such diabetes is at first reversible by weight reduction, but there is a tendency toward permanent establishment with increasing duration of the obesity.

Gynecological and Obstetrical Complications.—There have been a number of excellent studies on the influence of obesity in pregnancy.¶ The greatest antepartum hazard in the obese is toxemia. Douglas [57] found that 20% showed elevated blood pressure and 10% had specific toxemia of pregnancy. Chesley and co-workers [60] in a follow-up study of eclampsia found that the greater the height-weight ratio, the higher the incidence of toxemia in later pregnancies. It appears well documented that obese women have, on the average, significantly larger infants and hence a higher incidence of Caesarean sections and postpartum hemorrhage. On the other hand, they have a lower incidence of premature babies. Current studies reveal that

‖ Cited in Reference 55. Reference 56.

¶ References 57, 58, and 59.

in obese women there is no distinct variation in pelvic type or length of labor, no significant increased incidence of abnormal presentation or position, and no increase in fetal mortality. Dublin # reported an increased incidence of mortality from puerperal fever among obese women but was not able to give accurate figures.

Obesity has long been known to be frequently associated with menstrual disturbances. This has been one of the primary reasons that physicians have sought some endocrine disturbance to explain obesity. Rogers and Mitchell [61] studied 100 young women with menstrual disorders, infertility, and habitual abortion. Forty-three per cent of these were 20% or more overweight. Amenorrhea was the most frequent menstrual disorder, and 48% of these patients were obese, in contrast to 13% in the control group. Of 19 patients with functional uterine bleeding, obesity is the cause of amenorrhea or they have a common etiology. Emotional disorders, which may have been a factor in both, were not studied. The authors recalled that the hypothalamus has been experimentally found to play a role in regulation or reproductive function and that specific hypothalamic lesions may cause obesity. Thus both disorders may conceivably be the result of a hypothalamic disorder in some cases.

Disease of the Gall Bladder and Biliary Tract.—The habitus of the patient with gall bladder disease is known to all physicians as "fair, fat, female, forty." Dublin [16] found truly that the mortality from gall bladder and biliary tract disease in the obese female was three times the expected. In the obese male it was approximately twice the expected mortality. Mentzer [62] studied 612 postmortem sections of the gall bladder, of which 62% showed grossly visible disease. In this series 44 patients weighed more than 210 lb. (95.2 kg.) and 77% of these had lesions of the gall bladder (39% of these had stones and 38% had cholesterosis). He further demonstrated that the proportion of gall bladder disease increased with increase in body weight. Explanation of the relationship between obesity and gall bladder pathology is not readily apparent. With the high incidence of gall stones and cholesterosis one might suspect that the high serum cholesterol frequently associated with obesity may be an interrelating factor.

Arthritis.—Attention has often been called to the fact that osteoarthritis and obesity coexist.[63] In a study of 172 cases of "atrophic arthritis" Matz [64] found that only 40.1% of the patients were of stocky build. Harmon,[65] in a study of 94 cases of osteoarthritis of the hip, found that one-third had a significant degree of obesity. Stecker [66] found no significant association between obesity and Herberden's nodes, which are often considered to be the commonest manifestation of osteoarthritis. Certainly obesity must be acknowledged as an undesirable complication and an aggravating factor, for it undoubtedly increases the strain on the joints.

Englehart and Wagner [67] called attention to the triad of obesity, gout, and diabetes mellitus. They noted that both gout and diabetes have a hereditary tendency and both tend frequently to be associated with obesity. At present there is no evidence to suggest a common or related metabolic defect in gout and diabetes.

Cirrhosis of the Liver.—Although cirrhosis of the liver is listed in actuarial studies as rather high among the causes of death in obesity, this subject is rarely discussed in the literature. Dublin,[16] in his actuarial statistics, found that it had double the expected mortality in the male who was obese when insured. One might

References 16 and 23.

feel certain that if a follow-up study had been available just prior to death, a large per cent of these patients would have exhibited the typical emaciated appearance so common in advanced cirrhosis. Kelly [68] reported four cases of portal cirrhosis in nonalcoholic obese patients in which a unique hemorrhagic feature tended to predominate. This hemorrhagic tendency was not associated with thrombocytopenia or prothrombin deficiency. Malnutrition is acknowledged to play a role in the pathogenesis in portal cirrhosis. However, this need not be accompanied by undernutrition. Thus obesity can and does at times exist with advanced portal cirrhosis.

Cancer.—When all forms of cancer are taken as a group, the actuarial data reveal no increased mortality among the obese. However, the incidence of cancer of the liver and gall bladder appears to be significantly above the expected for both males and females.[16] This may simply be a reflection of the increased incidence of chronic gall bladder disease and cirrhosis among the obese. Hildreth [69] published a five-year follow-up study of carcinoma of the cervix uteri. He found that the obese group of 24 patients had a five-year survival rate of only 37.5%, as compared with a 54% survival rate in the nonobese. Most of these patients were treated with both x-rays and radium. He suggested that the technical factors encountered in irradiation of the obese were responsible for the increased mortality.

Surgical Conditions.—It is common knowledge that obesity tremendously increases the technical difficulties in surgery, the commonest of which is the difficulty of obtaining adequate exposure. Frank [70] discussed the increased technical difficulties in the surgical treatment of cancer of the body of the uterus in the obese. Principally he found difficulty in packing the abdomen adequately to avoid contamination; also, the obese were not able to tolerate the high Trendelenburg position as long without respiratory embarrassment. Dunlop [71] called attention to the difficulties of obtaining adequate exposure to ligate all the collateral vessels in saphenous vein ligation in the obese. The morbidity of surgery is increased by the increased tendency for wound breakdown, thrombosis, etc. Baker and co-workers [72] found that postoperative venous thrombosis and pulmonary embolism were definitely commoner in the obese. He had a 4% incidence in those under 200 lb. (90.7 kg.) and an 8% incidence in those over 200 lb. Dublin [16] found that the mortality from appendicitis was twice the expected in the obese male and that the mortality of hernia and intestinal obstruction was 1.5 times the expected.

Miscellaneous.—Kerr and Lagen [73] described a "postural syndrome," which generally has its onset in the third decade with obesity in a relaxed person. In the fourth decade spinal-column deformities result from the strain of the excess weight on the spine. This results in a kyphosis which causes great respiratory embarrassment and produces the barrel chest of obstructive emphysema. Short and Johnson [74] found that obesity tends to decrease the vital capacity in normal persons. The mechanism here is probably simple mechanical restriction of respiratory movement. It is quite apparent that obesity might be expected to have adverse effects in patients with pulmonary emphysema.

Studies of the effect of obesity on renal disease are hard to find. Dublin,[75] however, reported a significantly higher degree of albuminuria and glycosuria in periodic health examinations among those overweight than among the normal-weight or underweight subjects. In a later review of actuarial data,[16] he reported the mortality of chronic nephritis among the obese to be 90% above the expected.

Keleman,[76] in a study of 100 successive adult patients with sinus complaints, found that 56% were 10% overweight or more (average 32.6 lb. [14.7 kg.] overweight). He suggests that obesity is a preconditioning factor in infections of the upper respiratory tract, due to the decompensation in the function of the airways. He theorized that the circulatory and respiratory apparatus which was established for a certain reasonable weight is unable to cope with the new situation of overweight.

Villasinor and co-workers [77] studied the blood picture in a group of 240 subjects with an overweight greater than 15%. They found the average hemoglobin in the male was 17.2 gm. and in the female 14.8 gm. In 5% of the patients they found a polycythemia (average, 23 gm. in the male patients and 18.7 gm. in the female) that could not be explained by chronic lung disease, congenital heart disease, or presence of a high altitude. Hypertension was found in 41% of those with polycythemia.

Dublin [16] reports the death rate from cerebral hemorrhage in the obese to be 90% above the expected. This probably is a reflection of the increased incidence of arteriosclerosis and hypertension in the obese.

SUMMARY

The literature is reviewed regarding the correlation of obesity with various pathological conditions and decreased longevity. There is well-documented evidence in some cases that such correlation exists. However, in no case have the reasons for the associations been conclusively demonstrated, and it should be emphasized that correlation does not always indicate causation. Obviously, more research in this field is needed to provide the answers. Clinical evidence is presented as to the advantage of weight reduction in arteriosclerotic heart disease, hypertension, diabetes, and other conditions. Pathological evidence is presented indicating that weight reduction reverses arteriosclerotic changes. A current publication by Dublin [78] demonstrates conclusively that in general "fat people who lose weight live longer." In his study there were 2,300 persons who were at first given substandard life insurance policies but later reduced sufficiently to rate a standard policy. There was a substantial lowering of the mortality (one-fifth in the males and one-third in the females) among those who reduced. Thus the physician has sufficient evidence vehemently to advocate weight reduction for all obese persons who entrust their health and well-being to his care.

Blue Ridge Sanatorium.

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EVOLUTION OF CHEMOTHERAPY IN TUBERCULOSIS

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> Take of new Milk two Gallons, distil it with Mint, Roman Wormwood, of each two Handfuls to a Gallon. Then take of Garden Snails, washed first in common Water, and then Small beer, half a Peck, of Earth worms slit and wash'd a Pint, of Angelica a Handful and half, Agrimony, Betony, Rue of each a Handful. Put the Herbs in the bottom; upon these lay the Snails and Earthworms, and upon the top of all lay of Shavings of Hartshorn half a Pound, of Cloves an ounce, of Saffran three Drams, Infuse them in two Quarts of Syder, and a Quart of the best Malaga Sack, and then distil them in ordinary Still. These Liquors must be drank plentifully.
>
> For the cure of consumption in the second degree. SIR RICHARD MORTON—1720.

THE SPECIFIC agent in the etiology of tuberculosis was demonstrated by Koch in 1882, and shortly after this discovery the search for an antibacterial agent to combat this disease was initiated. This search may roughly be divided into an age of darkness, a renaissance, and a present period of progress. It is the purpose of this discussion to describe the assaults in these various periods, resulting in the denting and final penetration of the armor of the acid-fast destroyer.

As early as the 15th, 16th, and 17th centuries, arsenic, gold, mercury, iodine and iodides, cod liver oil, and creosote were employed in the treatment of pthisis.[1] In 1893 the intravenous injection of 5% cinnamylic acid (a constituent of balsam of Peru) was tried and injections of thymol and menthol employed which were thought to exert suppressive effects on the disease. Yet in that age of therapeutic darkness, some very interesting experiments were carried out, which, in the light of our present knowledge, might well be mentioned here. About 70 years ago, there appeared in the literature the report of the treatment of tuberculosis by inhalation of an apparently nonpathogenic organism known as Termobacterium. The patient was to inhale the contents of a bacterial culture of this organism by use of an atomizer, and it was claimed that Termobacterium replaced the tubercle bacilli in the sputum. In 1912 it was announced by Rappin that filtrates of broth cultures of Bacillus subtilis, B. mesentericus, and B. megatherium would strongly inhibit in vitro growth of tubercle bacilli, and shortly thereafter a report appeared relating an experiment in which "several guinea pigs which had been previously infected with tuberculosis were injected with the filtered cultures of B. mesentericus, and one animal lived more than 21 months in perfect health, another which died in 9 months put on weight regularly and at necropsy showed no lesion except a swelling at the site of inoculation" (!). These results, however, were not confirmed, and the general approval of the medical profession was not granted with regard to treatment of clinical cases with these filtered broths. Nevertheless, these efforts might be thought of as the first experiments in antimicrobial investigation in treatment of tuberculosis.[1]

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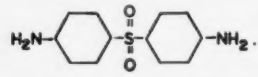
In the fruitless period from 1920 to 1930 attention was directed to the investigation of dyes, such as methylene blue, which was felt to act by penetrating the center of the tubercle, and to further studies of the effect of heavy metals, whose administration was to stimulate the immune forces of the host.* An observation was also made, about that time, that the vapors of volatile oils, such as peppermint, clove, and eucalyptus, could restrain growth of cultures of tubercle bacilli. In the early 1930's the use of intravenous gold was developed by the Danes [3] and considerable material appeared in the literature relative to its use. Regression of pulmonary lesions was reported with use of such gold preparations as gold sodium thiosulfate,† and the mode of action was claimed by some to be directly on the tubercles, by others to be indirect, by stimulation of the reticuloendothelial system. In this country, however, Amberson, Pinner, and McMahan concluded that the administration of gold had no beneficial effect on the disease. The use of various other substances was tried during this period, and there were reports regarding the oral administration of sodium tannate,[7] intravenous use of ferric chloride,[8] and inhalation of crotonaldehyde fumes. In each case reports were made of histologic changes in tuberculous disease, with these medications, consisting of fewer tubercles, less caseation, and an increase in fibrosis.

With the advent of the recognition of the effect of the sulfonamides in bacterial infections, the chemotherapy of tuberculosis entered its renaissance period.‡ In vitro studies showed that sulfanilamide, sulfathiazole, and sulfapyridine produced a certain inhibitory effect upon growth of virulent human tubercle bacilli. The clinical use of these drugs resulted, of course, in failure, but occasionally they were felt to benefit endobronchial lesions slightly. Nevertheless, these attempts lent great impetus to investigation and research with the sulfone drugs, particularly derivatives of diaminodiphenylsulfone  . These drugs were actually the first to arrest and permit healing of tuberculosis in any experimental animal. As a result of this effect on tuberculosis, they were applied to treatment of leprosy, the other important mycobacterial disease, and are to this day the standard and most effective remedy for this illness. Unfortunately, the sulfone drugs did not prove significantly effective in the treatment of human pulmonary tuberculosis. One of the first of this group of drugs to be evaluated was glucosulfone sodium (Promin). Work in 1940 [11] showed glucosulfone sodium to prevent guinea pigs in a large per cent from developing extensive tuberculous lesions after inoculation, and in some instances to give complete protection. In proper dose this sulfone was found to keep tuberculous infection in guinea pigs under suppression indefinitely, but when its use was stopped the animal died of its disease. Glucosulfone sodium proved very toxic, causing hemolytic anemia, agranulocytosis, drug rashes, and fever. This led to the search for less toxic sulfone derivatives and brought forth sulfoxone sodium (Diasone) and thiazolsulfone (Promizole).§ The former proved

* References 2 and 4.

† References 5 and 6.

‡ References 9 and 10.

§ References 12 and 13.

too toxic to be of practical clinical use. The latter was shown to give the same results in guinea pigs as twice the dose of glucosulfone sodium. It was used, however, to a certain extent in treatment of tuberculous diseases of the skin and lymph nodes and in tuberculous draining sinuses. Thiazolsulfone in combination with other drugs is still in use by some pediatricians in treatment of miliary tuberculosis and tuberculous meningitis.

In January, 1944, Schatz, Bugie, and Waksman [14] announced the discovery of streptomycin, and a new age of progress in treatment of tuberculosis had begun. This agent was described as derived from a sporulating and aeromycelium-forming species of actinomycete, Streptomyces griseus, in the hydrochloride form having an approximate chemical formula of $C_{21}H_{39}N_7O_{12}.3HCl$. With this weapon the attack was pressed with greater vigor, and without question the work with streptomycin of Hinshaw and Feldman, which began in 1944 [15] and produced the first evidence that streptomycin was a promising drug in tuberculosis, stands out as an imposing landmark along the ever-shortening trail to eventual eradication of tuberculosis. In 1945, these workers conducted a monumental experiment,[16] in which guinea pigs were inoculated with Mycobacterium tuberculosis 48 days before treatment. Twenty-four hours before treatment with streptomycin was started, liver biopsies were done on each animal to provide data as to the state of infection of each animal. After 166 days, 70% of the untreated animals had died but of those receiving streptomycin only 8% had died. All the untreated controls showed severe disseminated tuberculosis at necropsy, while of those under treatment 52% showed no tuberculosis grossly or microscopically. Shortly thereafter, Youmans demonstrated the suppressive action of streptomycin on tuberculous infection in mice.[17] Steenken at a later date confirmed the effect of the drug in guinea pigs.[18] It was also shown by Steenken at that time that the early dissemination of tubercle bacilli in the normal guinea pig is not influenced by streptomycin and that, although streptomycin limits the progression of tuberculous lesions in the guinea pig, lesions also progress despite adequate therapy, until acquired host resistance develops, as shown by the development of skin hypersensitiveness.[19]

The potency of streptomycin soon became further apparent as reports appeared with reference to histologic changes occurring under treatment with this drug. In 1945, Hinshaw || was the first to use streptomycin clinically, to recognize its known toxic and therapeutic effects,[23] and to report the histopathologic picture of healing of human tuberculosis under streptomycin therapy, with reduction of perifocal reaction in lung around fresh or healing foci, absence of caseation and fibrotic change, and clearing of exudative lesions by resolution.

With the groundwork laid, the tedious, but gratifying, work of the evaluation of the clinical importance of streptomycin in tuberculosis began. In this problem the American Trudeau Society and the Veterans Administration, Army, Navy, and Public Health Hospitals worked together in one of the greatest cooperative efforts in the history of clinical medicine. The special types of tuberculous infection in which streptomycin was of particular value soon became apparent. Very encouraging results began to be announced in treatment of miliary tuberculosis and meningitis. Tuberculosis laryngitis, tracheobronchitis,¶ and enteritis [24] also appeared to

|| References 20-22.

¶ References 21 and 22.

respond well to such therapy. Rapid deference and disappearance of symptoms in 48 to 72 hours was noted in some patients with tuberculous pneumonia under streptomycin therapy. Good results were noted in the chronic disseminated nodular type of tuberculosis,[25] but, unfortunately, the vast numbers of patients with caverno-caseous tuberculosis showed generally poor results. Today we feel that streptomycin therapy is perhaps universally indicated in tuberculotherapy but is most effective in mucosal tuberculous lesions, such as endobronchial tuberculosis, tuberculous laryngitis, and enteritis; rather effective in tuberculous adenitis and draining sinuses; effective in peritonitis and exudative pulmonary lesions without lung destruction, and less effective, but often curative, in bone and joint tuberculosis and miliary tuberculosis and meningitis.

Soon came the announcement of the use of dihydrostreptomycin.# Dihydro-streptomycin is prepared by catalytic hydrogenation of streptomycin. It differs from streptomycin only in having a hydroxyl instead of a carbonyl group in the streptobiosamine portion of the molecule. Guinea pig experiments showed that the antituberculous potency of dihydrostreptomycin was equal to that of streptomycin but was without effect on streptomycin-resistant bacilli. It was also seen that in humans dihydrostreptomycin was of the same range of antimicrobial action as streptomycin and could be well tolerated by patients hypersensitive to streptomycin.

Soon the toxicity of these potent agents became evident. With their administration, fever and eosinophilia were noted, renal damage occurred, a mild dermatitis was seen in 18% of cases, and in 1.5% there was an exfoliative dermatitis. But most important was the evidence of damage to the eighth cranial nerve, dihydro-streptomycin affecting chiefly the auditory branch, while streptomycin influenced the vestibular division. The degree of toxicity was found to depend largely on blood levels of the drugs, which, in turn, were influenced by dosage and renal function. Histologic studies done in animals who suffered streptomycin intoxication show atrophic changes in cells of the semicircular canals. It was found that varying degrees of vestibular dysfunction, as evidenced by caloric tests, were shown in the absence of symptoms [22] and that once damage had occurred it was reversible in only 2% of cases. Today we know that if streptomycin is given in 1.0 gm. daily doses over a period of 120 days approximately 25% of patients will show vestibular changes and that in the case of dihydrostreptomycin 10 to 20% of patients will undergo some hearing loss. It has been shown in cats that the use of equal amounts of streptomycin and dihydrostreptomycin in composing the dose of an antituberculous agent may result in considerably less toxicity than the use of either drug alone.[29] In the treatment of 35 patients with streptomycin-dihydrostreptomycin mixtures in doses of 1 gm. per day over periods of 120 days, neither auditory nor vestibular nerve toxicity was demonstrated.[30]

As more work was done the great protective value of these drugs when used for purposes of coverage at the time of surgery on tuberculous pulmonary tissue became apparent,* and today streptomycin is believed to be almost routinely indicated whenever and wherever tuberculous tissues are incised or excised.

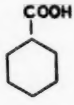
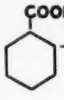
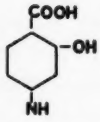
The clinical bacteriologist has played a great part in development of our knowledge of streptomycin, its characteristics and behavior. Very soon after the initiation

References 26-28.

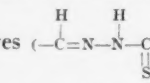
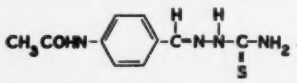
* References 31 and 32.

of its use the phenomenon of emergence of resistant strains of tubercle bacilli was noted by Youmans.[33] This has been explained on a "survival of the fittest" basis. It is believed that in the normal reduplication of tubercle bacilli mutated forms are constantly occurring. Under the influence of streptomycin most bacilli either are prevented from reproducing or are destroyed by the bacteriostatic action of the streptomycin. However, the occasional mutated forms that natively resist continue to divide and soon replace the dying population, resulting eventually in a completely resistant nation of organisms.[34] If streptomycin be given alone for 120 days in a dose of 1.0 gm. per day, resistance can be expected to develop in the usual case at the rate of 20% of the bacterial population per month. It has been noted that streptomycin resistance develops much more rapidly in treatment of cavernocaseous disease than of purely exudative disease. If we apply the work of Kahn[35] to this phenomenon, interesting speculation results. Kahn has shown that if tubercle bacilli are cultured on solid media they proliferate by simple fission. If grown in liquid media, the organisms pass through a developmental cycle of complex nature, in which many mutations are possible. If we consider an exudative lesion as similar to tubercle growth on solid media and cavernous disease as growth in liquid media (for Bogen has shown that good concentrations of streptomycin can be found in tuberculous cavities), it may be understood why more rapid resistance develops in disease in which cavitation is predominant. Another, and perhaps more important, factor which has been pointed out in recent work is that of the very rapid multiplication of tubercle bacilli in cavernous disease. With rapid reduplication there will be, of course, a greater number of resistant forms. However, it appears that much more investigation must be done before these phenomena are completely understood.

Progress in the antibiotic therapy of tuberculosis continued, and in 1949 neomycin was discovered, which is as active against the tubercle bacilli as streptomycin and of low toxicity in animals, but whose existence in treatment of humans was short-lived, owing to its pronounced ototoxic and nephrotoxic actions.[36]

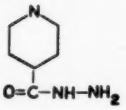
Meanwhile, in Sweden, extensive investigations were being completed with *p*-aminosalicylic acid, a tuberculostatic agent.[37] For many years experiments had been carried out, using the microrespiration apparatus of Warburg, on the oxygen uptake and requirements of the tubercle bacillus. It was observed in 1940 that benzoic acid  greatly increased oxygen consumption of tubercle bacilli and by so doing apparently inhibited the growth of these organisms. The addition of a hydroxyl group at the meta position enhanced this action and resulted in salicylic acid  . Through further addition of an amine group, the potent *p*-amino-salicylic acid  was formed. PAS is rapidly absorbed from the gastro-

intestinal tract and diffuses equally into all tissues except the spinal fluid. It can be given intravenously in neutral solution. The usual salicylate effects, such as sweating, tinnitus, and direct antipyretic effect, are not seen with this compound. Its chief toxic effects have been nausea, vomiting, and diarrhea. Perhaps the greatest advantage in the discovery of PAS has been in its combined use with streptomycin in prevention of emergence of resistant forms of tubercle bacilli. It has been found that the above combination of drugs reduces the development of resistant forms to a rate of 4% per month, as compared with 20% per month with streptomycin alone. Also, the use of streptomycin in the above combination on a twice-a-week dosage schedule has been found to be almost negligibly toxic, yet effective, in common forms of tuberculosis. This makes possible prolonged treatment of a year and over, as is indicated in the usual case of tuberculosis. It can be said almost without exception that whenever streptomycin is used in tuberculotherapy that PAS should be administered concurrently.

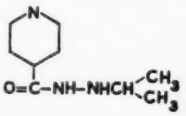
In Germany, since 1946 investigation has been under way with the thiosemicarbazone derivatives (). The sulfur atom was found to be important with regards to antitubercular activity. Many thiosemicarbazone derivatives have been investigated, and it has been noted that the substitution of groups at the nitrogen atoms of the open chain results in a decreased antibacterial action, while addition of benzene ring with radicals in the para position results in increased action. A widely investigated thiosemicarbazone was amithiozone  . The best effects of the thiosemicarbazones have perhaps been seen in tracheobronchitis. These drugs have not been satisfactory in controlling miliary tuberculosis and meningitis.[38] The thiosemicarbazones have also been found to be somewhat toxic in clinical use, with hemolytic anemia and agranulocytosis reported, as have been liver damage, albuminuria, gastric irritation, headache, conjunctivitis, and urticarial reactions. These agents have not been used as enthusiastically as they have been in Germany and have not in this country found a permanent place in the spectrum of antituberculous drugs.

As further work in antibiotics took place, viomycin, a derivative of Streptomyces floridae, entered the picture. There is no question as to the potent antituberculous action of this antimicrobial agent. This has been well documented in rabbit experimentation. It is also very effective against streptomycin-resistant tubercle bacilli; however, to date, toxicity in humans has limited its use. This has been manifested by tinnitus and disturbed vestibular function, hypersensitivity reactions, and renal irritation, as manifested by albuminuria, hematuria, and cylindruria. It is of interest also to point out that marked electrolyte disturbances were occasionally noted during the administration of large doses of viomycin, consisting of hypocalcemia, hypokalemia, hypophosphatemia, hypochloremia, and alkalosis. Interest in viomycin will probably be renewed with the recent development of more purified products, which have lately been used in treatment of streptomycin-resistant postsurgical cases.

Perhaps the most recent drugs showing potent antituberculous action are the nicotinic acid amide derivatives [39] and nicotinamide-like drugs. The mode of action of these drugs is not precisely known, but they may affect the metabolism of the tuberculosis organism by inhibition of nucleotidase. Of this group, perhaps isoniazid



(isonicotinic acid hydrazide, Nydrazid, INH, Rimifon) and its isopropyl derivative, iproniazid,



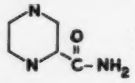
(Marsilid), have been greeted with most enthusiasm.† These potent agents will inhibit growth of the tubercle bacillus in vitro in a concentration of 0.02 γ per cubic centimeter. Both these drugs show considerable antituberculous effect in guinea pigs and will inhibit tuberculosis at a dose of 2.0 mg. per pig per day. They are of generally low toxicity in therapeutic doses. High doses have been shown to exert somewhat of a parasympathetic-blocking action, and urinary retention and slowing of intestinal peristalsis have been noted. Rarely vertigo and convulsions have been reported. Toxic reactions with isoniazid have generally been of the acute variety and have not been observed in parenchymatous organs or bone marrow.[41] Iproniazid, however, has been found to be appreciably more toxic than isoniazid, and blood dyscrasias of hemorrhagic nature have been noted. Also of significance has been the appearance of psychoses, some of irreversible nature, associated with the administration of this drug. For these reasons, the clinical use of iproniazid will probably be short-lived. Of particular interest is a report [42] dealing with the treatment of 44 patients with acute febrile caseous tuberculous pneumonia, some of which were treated with isoniazid and others with iproniazid for 4 to 15 weeks. Rapid and marked reversal of original toxic states, with reduced cough, expectoration, and sputum contents was observed. However, the use of the above agents in advanced fibrocaseous disease is of questionable value from the long-range viewpoint. The Medical Research Council of Great Britain has reported on the use of isoniazid alone administered over a three-month period in a large series of cases.[43] They concluded that isoniazid given alone is not more effective than streptomycin plus PAS. Again the problem of resistance arises. When isoniazid is used alone, bacillary resistance develops at the rate of 10% the first month and 40% the second month, and by the third month 70% of the bacterial population is resistant.‡ The combining of isoniazid with other antituberculous drugs in an attempt to delay resistance, and for the production of additive or synergistic effects, has been given clinical trials. Investigators of the Medical Research Council of Great Britain [45] conclude that, as used over a three-month period, streptomycin plus isoniazid is clinically the most effective of the treatments studied, although its superiority to streptomycin plus PAS is not great. Reports vary at present as to whether the combining of isoniazid with streptomycin can appreciably delay the emergence of isoniazid-resistant forms of tubercle bacilli. British reports [45] indicate that the combination of isoniazid and streptomycin, as

† References 40 and 41.

‡ References 43 and 44.

given over a three-month period, may reduce resistance to isoniazid to 13%. Such results have not been duplicated in other recent trials,[42] in which the combination of the above two drugs has failed to show significant delay of development of resistance to isoniazid. The use of streptomycin plus PAS plus isoniazid has not as yet been extensively investigated but may prove to be synergistically an extremely potent combination.

Of particular importance is the ability of the isonicotinic acid derivatives to penetrate the spinal fluid in high concentration, which, of course, adds a great weapon in combating tuberculous meningitis.

Under investigation also are derivatives of pyrazinoic acid (pyrazinamide [Aldinamide], ).[46] Early work done with the compound shows that its use may be limited, due to very rapid emergence of resistant forms of tubercle bacilli. On an experimental basis, cortisone and corticotropin (ACTH) are being used for their lytic effect on connective tissue, in the hope that such drugs as streptomycin and PAS might better penetrate areas of encased tubercle bacilli. Preliminary reports on this therapy are inconclusive. Oxytetracycline (Terramycin) in large doses has also been shown to inhibit growth of tubercle bacilli, but only further work will establish its clinical application.

So we have followed the chemotherapy of tuberculosis from the darkness of the 15th and 16th centuries to the perhaps dim but ever-increasing light of today. The torch has certainly never burned brighter, and as its rays penetrate and wipe away the shadows, so may man eventually be freed from the affliction of tuberculosis.

400 29th St.

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Case Reports

ACQUIRED HEMOLYTIC ANEMIA ASSOCIATED WITH HEMOCHROMATOSIS

J. K. SIDDOO, M.D.
VANCOUVER, CANADA

THE COEXISTENCE of acquired hemolytic anemia and hemochromatosis has not been reported previously to our knowledge. Recently, however, a case of congenital hemolytic anemia and hemachromatosis has been described.[1]

It is important to differentiate between hemosiderosis and hemochromatosis. Hemosiderosis is the excessive deposition of hemosiderin in the tissues, due to several possible causes. Hemochromatosis is a rare, chronic, progressive disorder of iron metabolism, characterized in the early stage by an abnormal deposition of hemosiderin in the skin and viscera, followed by fibrosis of the liver and pancreas and, in the fully developed case, the presence of diabetes mellitus. Hemosiderosis may result from transfusions, administration of intravenous iron, or excessive breakdown of red blood cells in hemolytic anemias. Hemochromatosis is an idiopathic condition, and it is a moot point as to whether transfusions or diet may be the cause of certain instances.*

The case presented fulfills the above criteria for idiopathic hemochromatosis, i. e., hemosiderosis and fibrosis, except for the absence of diabetes mellitus. In addition, there was hematologic evidence of an acquired hemolytic anemia of an immunologic type.

REPORT OF A CASE

D. T., a 47-year-old white man of Scottish origin, was admitted to the Vancouver General Hospital on Feb. 27, 1953, with the entrance complaints of progressive pigmentation and weight loss of six months' duration and increasing dyspnea and abdominal pain of two weeks' duration. He had been in his usual state of health until August, 1952, when he developed pigmentation of the face, hands, and elbows. Subsequently, he became listless and apathetic and began to lose weight. In January, 1953, he vomited small amounts of bright red blood. By mid-February, 1953, he was having frequent episodes of substernal and upper abdominal pain associated with extreme breathlessness on exertion, which necessitated his admission to the hospital.

He had suffered with gaseous discomfort for many years and, since 1948, had consumed, weekly, one bottle of a proprietary medicine containing acetophenetidin (Phenacetin) and acetanilid. His alcoholic intake had averaged three to four glasses of beer daily for many years.

He had had chronic osteomyelitis since 1945, following a fracture of his left tibia, which had been treated with Roger Anderson fixation. In 1950, coagulase-positive Staphylococcus aureus was cultured from this site. At this time his hemoglobin was 89% (12.9 gm.). In December, 1951, a sequestrectomy was performed. In August, 1952, Staph. aureus was again cultured from the same site and the tibia was saucerized. At this time it was observed that the patient had blue-gray pigmentation of the mouth, face, hands, and elbows. Methemo-

From the Department of Pathology, Vancouver General Hospital.

* References 2 and 3.

globinemia was excluded by spectroscopic examination of the blood. The liver and spleen were not palpable. On this admission, both the hemoglobin and total serum bilirubin were normal (hemoglobin, 13.8 gm.; total serum bilirubin, 1.1 mg. per 100 cc.).

Physical examination revealed a well-developed well-nourished white man with diffuse brownish pigmentation of head, neck, forearms, and palm creases. The temperature was 101 F. The pulse rate was 108 per minute. The blood pressure reading was 120/70. Relevant findings on examination were as follows: jaundiced sclerae, pallor of mucous membranes of mouth, normal cardiovascular system, splenomegaly, and no hepatomegaly.

Laboratory Investigation.—Total serum bilirubin was 4.0 mg. per 100 cc.; fecal urobilinogen, 1,531 mg. in a 24-hour specimen; urine urobilinogen, 2.3 mg. per 100 ml. Spectroscopic examination of the urine revealed no abnormal pigments. Total protein was 5.9 gm. per 100 ml.; albumin, 3.4 gm. per 100 ml.; globulin, 2.5 gm. per 100 ml.; thymol turbidity, 1 unit, and thymol flocculation, a trace. The electrocardiogram showed evidence of acute coronary insufficiency. Methemalbumin was present in the blood serum, but no methemoglobin was detected. Skin biopsy showed the presence of hemosiderin. No glucose-tolerance test was done. The urine did not show reducing substances. Hematologic examination (March 3, 1953) showed red blood cells, 2,100,000 per cubic millimeter; hemoglobin, 49% (7.0 gm.), and white blood cells, 6,350 per cubic millimeter. Differential count showed 63% neutrophiles, 9% eosinophiles, 1% basophiles, 2% staff cells, 1% myelocytes, 22% lymphocytes, and 2% monocytes. Platelets were 74,000 per cubic millimeter; reticulocytes, 6.2%; haematocrit level, 20%; mean corpuscular volume, 95 cu. μ; mean corpuscular hemoglobin, 33 $\mu\gamma$; mean corpuscular hemoglobin concentration, 35%. The plasma was greenish yellow. The red cell morphology showed 2+ anisocytosis, 1+ macrocytosis, and 3+ microcytosis (microcytes appeared hyperchromic). No hypochromia was noted. Nucleated red blood cells, polychromasia, basophilic stippling, and Howell-Jolly bodies were present. The sedimentation rate was 100 mm. in an hour. The prothrombin activity was 48% of normal. Direct and indirect Coombs tests were positive. Relevant findings on iliac puncture were 16.3% late normoblasts, 28.0% intermediate normoblasts, 18.0% early normoblasts, and 2.3% proerythroblasts. The hematologic report was as follows: "The blood findings are consistent with acquired hemolytic anemia, and there is nothing in the hematologic investigation which gives a clue to the character of the cause." Conclusions reached as a result of serologic investigation were that the patient had an acquired hemolytic anemia of the warm type, which followed the reaction pattern 4++ of Davidsohn.[4]

Results of Tests of Serum for Circulating Antibodies (April 25, 1953):

Patient's blood group A Rh positive

Hemolysins

None demonstrable when incubated one hour and overnight in either saline or albumin dilutions at 37 C., 5 C., or room temperature against O Rh-positive or patient's own washed cells

Agglutinins

None demonstrated, as above

Blocking antibodies

At 37 C., incubated one hour against O Rh-positive cells: none demonstrable

At 37 C., incubated one hour against own cells: titer 1:16

At room temperature, incubated one hour against O Rh-positive cells: none demonstrable

At room temperature, incubated one hour against own cells: titer 1:8

At 5 C., incubated one hour against O Rh-positive cells: titer 1:8

At 5 C., incubated one hour against own cells: titer 1:32

Indirect Coombs titration for third-order antibodies against O Rh-positive cells: titer 1:32

Indirect Coombs titration for third-order antibodies against own washed cells: titer 1:16,000

Diagnosis.—The clinical diagnosis was acquired hemolytic anaemia.

Clinical Course.—The patient was given four courses of corticotropin (ACTH) (total of 425 mg.) without any improvement. During the entire illness he received 4 liters of whole blood and these only in the last two months of life (March and April, 1953). His final admission was on April 20, 1953. Twelve hours prior to death the patient vomited more than 2 liters of red blood. He died on April 27, 1953.

Postmortem Examination.—The autopsy was done 18 hours after death. The face and neck were grayish. There was diffuse brown pigmentation of the hands, forearms, genitalia, and legs and of the scar over the left tibia. The thyroid was normal. The right pleural cavity contained 100 cc. and the left, 200 cc. of clear straw-colored fluid. The right lung weighed 525 gm., and the left, 500 gm. The cut surface of both lungs was brownish. Some small pulmonary arteries contained dry grayish-red emboli which projected above the cut surface. The main pulmonary arteries contained no emboli. The heart weighed 500 gm. No infarcts were present. There were white linear areas of fibrosis throughout the myocardium of the left ventricle. The coronary arteries showed marked atherosclerosis but no occlusion. The peritoneal cavity contained 1,000 cc. of clear straw-colored fluid. There were over a dozen small dark-brown firm paraortic lymph nodes, measuring 5 mm. by 7 mm. each. Esophogeal varices were present. A ruptured varix was seen in the esophagus 4 cm. from the cardiac end of the stomach. The stomach was filled with dark clotted blood. Along the lesser curvature of the stomach midway between the cardia and pylorus was an old healed ulcer, measuring 2 by 3 cm., with no evidence of recent bleeding. The remainder of the gastrointestinal tract also contained dark red blood. The liver weighed 2,000 gm. The external surface was dark-brown, extremely firm, and nodular, the nodules measuring up to 1 cm. The organ was cut with difficulty, and the exposed surface showed complete loss of the normal lobular pattern, with replacement by dark brown nodules. In the center of the liver there was a round soft yellow nodule, measuring 2 by 2 cm., which had the appearance of a hepatoma. The gall bladder, bile duct system, and ampulla of Vater were normal. The pancreas was firm, dark-brown, and nodular. The cut surface was yellowish-brown and firm. The spleen weighed 670 gm. The external surface was smooth. Two infarcts, measuring 3 by 3 cm., were present. The cut surface was soft and dark red. The adrenals were normal. The right kidney weighed 225 gm., and the left, 250 gm. They appeared normal. The prostate was normal. The testes were not examined. The central nervous system was not examined. The ribs, vertebrae, and sternum contained abundant red marrow. Prussian blue tests for the presence of iron were carried out. The liver and pancreas were strongly positive. The spleen was faintly positive.

Microscopic Examination.—Prussian blue stain was used for the detection of hemosiderin. The liver showed advanced periportal fibrosis and enormous amounts of hemosiderin in the liver cells, Kupffer cells, and fibrous tissue. One section showed a hepatoma, with nodular collections of cells that varied in size, shape, and staining characteristics. The pancreas showed a slight degree of fibrosis and marked amounts of hemosiderin in the acinar tissue. The islets of Langerhans could not be identified, because of postmortem degeneration. The lymph nodes showed a moderate degree of fibrosis and enormous amounts of hemosiderin in the macrophages. The spleen showed some fibrosis and only minimal amounts of hemosiderin in the capsule, macrophages, and vessel walls. The thyroid showed a marked degree of fibrosis and large amounts of hemosiderin in the acinar cells and in the fibrous tissue. The skin showed small amounts of hemosiderin in and around the sweat glands; there were also increased amounts of melanin in the basal layer of the epidermis. The prostate showed no atrophy or fibrosis, and minimal amounts of hemosiderin were present in the acinar tissue. Large amounts of hemosiderin were present in the zona glomerulosa of the adrenal, and there were lesser amounts in the medulla. The heart showed moderate amounts of hemosiderin in the muscle cells, arranged in a spindle-shaped manner at both poles of the nucleus. The mucous glands of the bronchi showed large amounts of hemosiderin, but only minimal amounts were present in the alveolar walls of the lungs. The kidneys showed moderate amounts of hemosiderin in the proximal convoluted tubules and minimal amounts in the glomeruli. The vertebrae showed a greatly hyperplastic marrow and only minimal amounts of hemosiderin. Thus, the greatest amounts of iron were seen in the parenchymal cells of the liver, pancreas, and lymph nodes; mucous glands

of bronchi, and adrenal cortex, and there were lesser amounts in the sweat glands of the skin, the thyroid, prostate, heart, lungs, intestine, and kidneys. Minimal amounts were seen in the spleen and bone marrow. There was fibrosis of the liver, pancreas, lymph nodes, thyroid, and spleen.

Summary of Pathological Findings: (1) hemochromatosis, (2) hepatoma, (3) esophageal varices with rupture, (4) ascites, (5) chronic gastric ulcer, (6) arteriosclerotic heart disease, (7) infarcts of spleen, and (8) pulmonary emboli.

COMMENT

Three problems arise in the consideration of this subject, the etiology of the hemolytic anemia, the etiology of the hemochromatosis, and the relationship, if any, between the two.

The hemolytic anaemia, which was of an acquired immunologic type, might possibly be attributed to three causes, drugs, infection, and hemochromatosis.

Acute drug poisoning may produce hemolytic anemia.[5] This patient consumed great quantities of acetanilid and acetophenetidin over a period of five years. There are, however, two points against this hypothesis; first, the drugs were taken over a long period of time and, secondly, during hospitalization, when these drugs were discontinued, no improvement occurred.

In rare cases a coccus may exert a direct hemolytic effect on the red cells, resulting in an acute hemolytic anemia.[6] This man had chronic osteomyelitis of eight years' duration. The organism cultured on repeated occasions was Staph. aureus, coagulase-positive. We can neither deny nor accept this explanation, as no blood cultures were taken. There was, however, nothing either in the clinical picture or at autopsy to suggest pyemia or sepsis.

Hemochromatosis has never been described as a cause of hemolytic anemia. Watson and others,† however, have reported the occurrence of hemolytic anemia in association with liver disease, but no explanation has been offered.

In the etiology of hemochromatosis two causes must be considered, transfusions and diet. During the entire course of his illness this patient received a total of 4 liters of whole blood, containing approximately 2 gm. of iron. Assuming that the iron stores were further increased by hemolysis, the maximum amount of iron that could be transferred from the hemolysed red cells to the iron stores would amount to 1 or 2 gm.[9] This would result in a total of 4 gm. of iron in the body stores. Finch [9] has stated that probably more than 100 transfusions are needed before hemochromatosis can develop. Interesting observations have been made by several authors which indicate that an excessive amount of iron is absorbed in hemolytic anemia. Dubach and coworkers,[10] in studying iron absorption by the isotope technique, have shown that in hemolytic anemia more iron is absorbed that can be recovered from the peripheral blood. Granick [11] has stated that in various anemias, including hemolytic anemia, the lowered oxygen supply in the mucosal cells of the duodenum causes an increase in the amount of iron moving through the mucosal cell into the blood stream. However, it seems unlikely that transfusions were the cause.

Gillman and co-workers [8] have described deposition of large amounts of iron and fibrosis of the liver in South African natives using iron cooking pots and living on an inadequate diet, chiefly of corn meal. The dietary intake in this patient may

† References 7 and 8.

have been inadequate because of the consumption of moderate amounts of alcohol and the presence of a gastric ulcer. It might be postulated that dietary deficiency produced the cirrhosis of the liver, while the deposition of iron was secondary to the hemolytic anemia.

I conclude that the hemochromatosis was not related to the hemolytic anemia and that it was due to some long-standing disturbance of iron metabolism, of whose nature I am ignorant.

SUMMARY

The clinical and pathological findings in a case showing both hemochromatosis and acquired hemolytic anemia are presented. No cause has been determined for either condition, nor do they appear interrelated.

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News and Comment

ANNOUNCEMENTS

Gamma Globulin for Poliomyelitis.—Plans for the distribution of gamma globulin for use against poliomyelitis during the coming season have been sent to all State and Territorial Health Officers by the Public Health Service, Department of Health, Education, and Welfare.

The following procedures governing the distribution plans were transmitted to the Public Health Service by the Office of Defense Mobilization:

1. Forty-five percent of the supply of gamma globulin available for the prophylaxis of poliomyelitis will be set aside for the States and Territories in accordance with each State's proportionate share of the national aggregate number of reported poliomyelitis cases during the five-year period 1949-1953. Issuances to a State or Territory will be made upon request by the State or Territorial Health Officer.

2. Forty-five percent of the supply of gamma globulin available for the prophylaxis of poliomyelitis will be set aside for the States and Territories in accordance with each State's proportionate share of the total population (1950) under age 15 in counties which had annual crude poliomyelitis attack rates (based on 20 or more cases) at least four times the national poliomyelitis crude attack rate during any of the years 1949-1953. The population of a county will be included in this computation for each instance of such experience during the five-year period. Adjustments will be made for those areas participating in the vaccine field trial. Issuance to a State or Territory will be made upon request of the State or Territorial Health Officer.

3. Ten percent of the supply of gamma globulin available for the prophylaxis of poliomyelitis will be held as a contingency reserve for issuance to State and Territorial Health Officers on special request.

Poliomyelitis gamma globulin is being kept separately and is being issued separately from the gamma globulin furnished for the prophylaxis of measles and infectious hepatitis.

The first allotment of gamma globulin for use against poliomyelitis became available to all State health departments on April 7. The second allotment will be ready for distribution on or about June 1. State health departments have been instructed to submit requests for gamma globulin for use against poliomyelitis to Division of Civilian Health Requirements, Public Health Service, Department of Health, Education, and Welfare, Washington 25, D. C.

American College of Gastroenterology.—Final steps in the activation of the American College of Gastroenterology were taken by the Fellowship of the National Gastroenterological Association at a special meeting recently held in New York.

At this meeting, it was voted to transfer the membership of the National Gastroenterological Association, classified as to their present status, to the American College of Gatsroenterology. A transfer of all the assets, including the official publication, *The American Journal of Gastroenterology,* to the College was also voted upon.

The Officers of the College are Drs. Sigurd W. Johnsen, Passaic, N. J., President; Lynn A. Ferguson, Grand Rapids, Mich., President-elect; James T. Nix, New Orleans, First Vice-President; Arthur A. Kirchner, Los Angeles, Second Vice-President; C. Wilmer Wirts, Philadelphia, Third Vice-President; Frank J. Borrelli, New York, Fourth Vice-President; Roy Upham, New York, Secretary-General; A. Xerxes Rossien, Kew Gardens, N. Y., Secretary; Elihu Katz, New York, Treasurer, and Samuel Weiss, New York, Editor.

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The College will hold its first Convention in Washington, D. C., Oct. 25-27, 1954, in conjunction with the 19th Annual Convention of the National Gastroenterological Association.

Information concerning membership in the American College of Gastroenterology may be obtained by writing to the Executive Secretary, American College of Gastroenterology, 33 West 60th St., New York 23.

Newer Developments in Cardiovascular Diseases.—A course in Newer Developments in Cardiovascular Diseases will be given at The Mount Sinai Hospital, New York, Oct. 11-15, 1954, under the auspices of the American College of Physicians. As the title implies, the recent advances will be stressed. Dr. Arthur M. Master and Dr. Charles K. Friedberg will direct the course, and prominent cardiologists and cardiac surgeons will participate.

Course in Postgraduate Gastroenterology.—The National Gastroenterological Association announces that its Sixth Annual Course in Postgraduate Gastroenterology will be given at The Shoreham, in Washington, D. C., on Oct. 28-30, 1954.

The course will again be under the co-chairmanship of Dr. Owen H. Wangensteen, Professor of Surgery, of the University of Minnesota Medical School, who will serve as surgical coordinator, and Dr. I. Snapper, Director of Medical Education, Beth-el Hospital, Brooklyn, who will serve as medical coordinator.

Drs. Wangensteen and Snapper will be assisted by a distinguished faculty selected from the medical schools and Walter Reed Army Hospital, whose presentations will cover all phases of gastrointestinal diseases and problems.

The entire session on Friday, Oct. 30, 1954, will be given at the Walter Reed Army Hospital.

For further information and enrollment write to the National Gastroenterological Association, Department GSJ, 33 West 60th St., New York 23.

The National Institute of Mental Health Postdoctorate and Special Research Fellowships.—These Fellowships are a part of the over-all Fellowship program of the National Institutes of Health in the field of the medical and health sciences and related fields.

Fellowships are awarded to scientists in the medical, biological, behavioral, or social science disciplines who wish to obtain further research training and who wish to carry out a program of research. Training may be requested for research on clinical problems or on related problems in the basic scientific disciplines.

Postdoctorate Research Fellowships.—These Fellowships are awarded to qualified persons holding a Ph.D., M.D., or other equivalent degrees. The stipend is $3,400 a year plus a $350 allowance for dependent spouse and each dependent child. Postdoctorate Fellows must show evidence that they expect to follow a career of research. Awards are given for one year, but commitment for a second year will be considered when requested by the Fellow and sponsor. Stipends are increased $300 for the second year. Supply grants up to $500 in support of the Fellow's research may be awarded to the sponsoring institution.

Special Research Fellowships.—These advanced Fellowships are awarded to qualified applicants who have a doctor's degree or its equivalent, who have already demonstrated competence for research, and who desire specialized training either in their own field of research or in a related field. Stipends are determined individually by the Surgeon General.

Applications may be submitted at any time of the year. Notification will be given three to four months after receipt of the application.

For further information and application blanks write to National Institutes of Health, Division of Research Grants, Research Fellowships Branch, Bethesda 14, Md.

Feazel Laboratory for Study of Cerebral Circulation and Migraine.—A laboratory and clinic for the study and treatment of migraine, a cause of agonizing pain to millions of Americans, have been established in the Tulane School of Medicine by Miss Lallage Feazel, of Monroe, La.

Dr. Rufus C. Harris, president of Tulane University, announced that a gift of $20,000, to put the laboratory into operation, had been made by Miss Feazel and her father, former United States Senator W. C. Feazel, of Monroe and Shreveport, La.

To be known as the Feazel Laboratory for the Study of the Cerebral Circulation and Migraine, it will be included in the cardiovascular laboratories to be situated in the new addition to the Hutchinson Memorial Medical Building, now under construction.

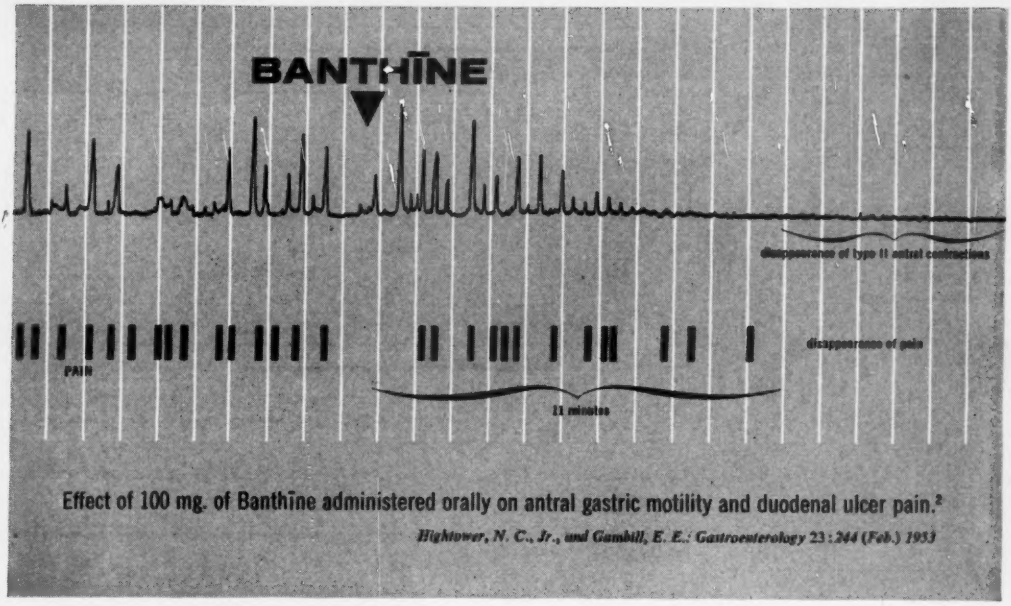
The laboratories will be under the direction of Dr. George E. Burch, the Henderson professor of medicine and chairman of the department of medicine at Tulane.

Dr. Burch pointed out that the association of the school of medicine with charity Hospital would allow studies to be made on a large number of patients with migraine.

He said that a clinic for treatment of patients suffering from this difficulty, to be maintained in connection with the laboratory, will probably be ready to begin service in July.

CORRECTION

In the third line of the article "Amyloidosis: Report of Three Cases with Some Considerations as to Etiology and Pathogenesis," by Dr. Albert Jackson (March issue, p. 494), the words "and diluted sulfuric acid" were omitted from the copy submitted. The second sentence of the article should read: "Later Virchow noted that this substance stained blue-black with iodine and diluted sulfuric acid and showed some similarity to starch."



Effect of 100 mg. of Banthine administered orally on antral gastric motility and duodenal ulcer pain.[2]

Hightower, N. C., Jr., and Gambill, E. E.: Gastroenterology 23:244 (Feb.) 1953

Banthine® Reduces Hypermotility and Hyperacidity in Peptic Ulcer

A recent evaluation of anticholinergic therapy in peptic ulcer emphasizes the fact that now the profession has at its disposal agents that are "effective in reducing both secretory and motor activity of the stomach."

The effect on motor activity is generally more pronounced and less variable than on secretion; pain relief is usually prompt; a high degree of effectiveness is noted in ambulatory ulcer patients.

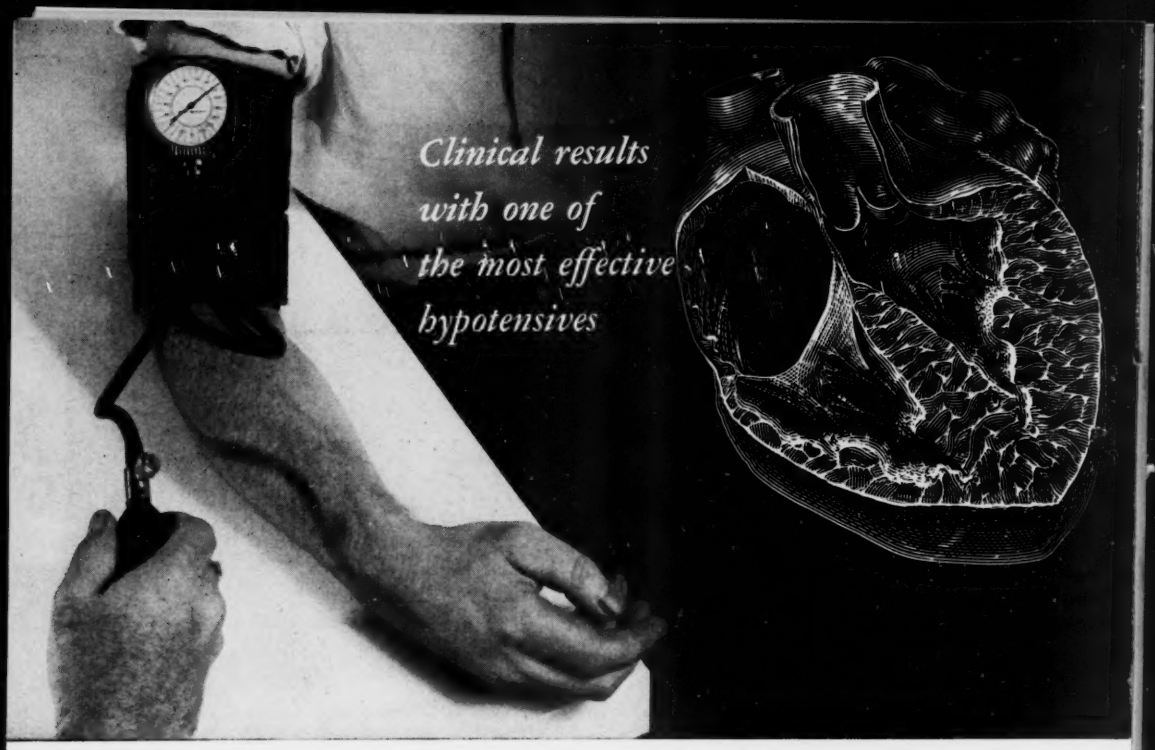
Ruffin, J. M.; Texter, E. C., Jr.; Carter, D. D., and Baylin, G. J.: J.A.M.A. 153:1159 (Nov. 28) 1953.

With its proved anticholinergic effectiveness, Banthine has been found extremely useful in the medical management of active peptic ulcer, whether duodenal, gastric or marginal.

The immediate increase in subjective well-being and the simplicity of the Banthine regimen assures patient cooperation. The recommended initial therapeutic dose is 50 or 100 mg. (one or two tablets) every six hours around the clock, with subsequent individual adjustment. The usual measures of diet regulation, rest and relaxation should be followed.

Banthine is effective in other conditions caused by excess parasympathetic stimulation. These include hypertrophic gastritis, acute and chronic pancreatitis, biliary dyskinesia and hyperhidrosis. Banthine is contraindicated in the presence of glaucoma and should be used with caution in the presence of severe cardiac disease or prostatic hypertrophy.

Banthine® bromide (brand of methantheline bromide) is supplied in scored tablets of 50 mg. and in ampuls of 50 mg. It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. G. D. Searle & Co., Research in the Service of Medicine.



Improvement in 67 to 72% of patients with hypertensive heart disease[1]

Together with significant reductions of elevated blood pressure in 80 per cent of outpatient hypertensives,[1] Methium therapy may result in substantial improvement in cardiac symptoms and signs.[1,2,3] Precordial pain, ventricular strain, heart failure and hypertrophy may all respond to careful treatment.[1,2,3] Actual myocardial damage, however, seldom shows any improvement (only 8 out of 44 in one study[1]).

With continued management, up to or beyond a year, blood pressure may be reduced and stabilized, and cardinal symptoms arrested or reversed, without any increase in dosage.[1]

As blood pressure is reduced, and even without reduction, hypertension symptoms have regressed. Retinopathy may disappear; headache, cardiac failure and kidney function may improve.

Methium, a potent autonomic ganglionic blocking agent, reduces blood pressure by interrupting nerve impulses responsible for vasoconstriction. Because of its potency, careful use is required. Pretreatment patient-evaluation should be thorough. Special care is needed in impaired renal function, coronary disease and existing or threatened cerebral vascular accidents.

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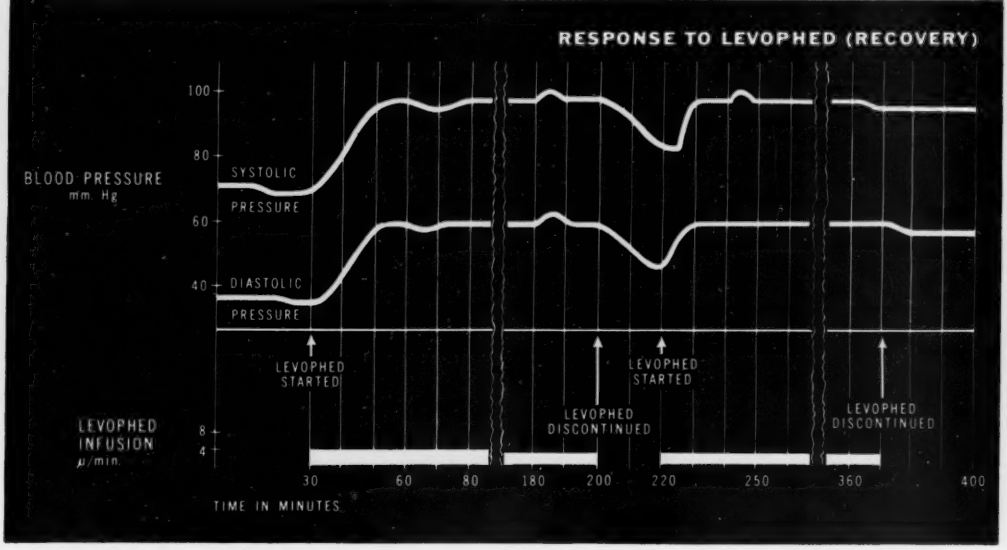

Reduction of Mortality

"...in correcting the state of shock we have enabled certain patients to recover from the initial episode, which otherwise gave every indication of culminating in death."[1]

Levophed infusion causes a striking rise in oxygen tension in areas of myocardial ischemia produced by coronary obstruction.[2] "It is therefore reasonable to suppose that the restoration of arterial pressure to a level consistent with an adequate coronary flow must limit the size of the infarct, save healthy myocardium, shorten the period of shock, and lessen the likelihood of congestive failure at a later date."[3]

"Severe cardiogenic shock demands therapy...the most efficacious method of treatment now available is use of vasopressor drugs."[4] "Current usage favors nor-epinephrine."[5]

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Lester M. Morrison, M.D., Los Angeles, in Rev. Gastroenterology, 20:744 (Oct.) 1953; abstract in J.A.M.A. 153:1580 (Dec. 26) 1953.

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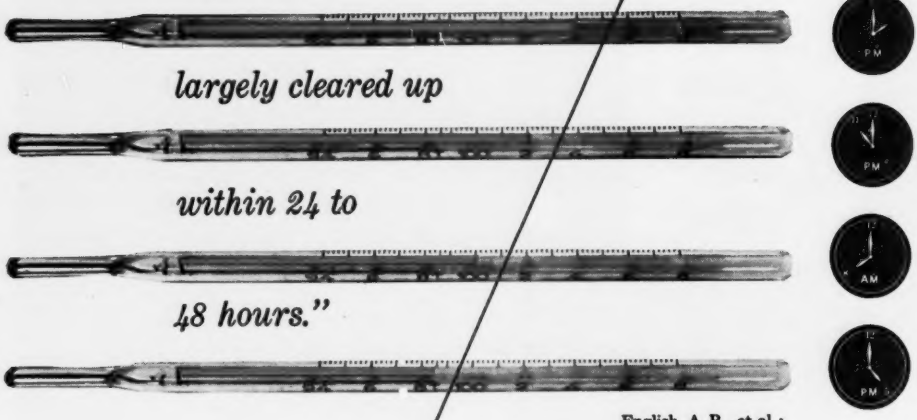

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English, A. R., et al.:
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C I B A *Summit, N. J.*

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